(54) Title: CRYSTALS OF FRAGMENTS OF CD40 LIGAND AND THEIR USE

(57) Abstract

The present invention relates to crystals of fragments of CD40 ligand, specifically, a soluble fragment of CD40 ligand (116-261). The invention relates further to uses of these crystals and the coordinates thereof to design, identify, optimize or characterize chemical entities having properties of interest.

# CRYSTALS OF FRAGMENTS OF CD40 LIGAND AND THEIR USE

The present invention relates to a crystalline form of a soluble fragment of the extracellular domain of human CD40 ligand, and more particularly, to a crystal of a CD40L fragment containing residues Gly116 to Leu261 ("sCD40L(116-261)") and its structure, obtained by x-ray diffraction. In addition, this invention relates to methods of using a crystal structure of CD40L, or a fragment thereof, and, specifically sCD40L(116-261), to design, screen, and optimize compounds that affect CD40L activity.

## BACKGROUND OF THE INVENTION

The immune system consists of many complex processes, which, together, protect the body against toxic and/or pathogenic agents. Generally, an immune response is initiated when certain cells within the body recognize the toxic or pathogenic agents. The response is then communicated through any of a series of means, such as cell-cell contact or soluble mediators, to other cells involved in the immune response.

CD40 ligand ("CD40L") has been shown to mediate functional T and B cell interactions involved in the immune response. The term CD40L refers to a genus of polypeptides which are capable of binding CD40, or homologs thereof. In fact, the interaction of CD40L with CD40 expressed by B-cells is the principal molecular interaction responsible for T cell contact dependent induction of B cell growth and differentiation, to antigen specific antibody production. Binding of T-cell CD40L to its counter-receptor CD40 expressed on the surface of B lymphocytes results in pleiotropic activities, including activation of antibody isotype switching, prevention of B cell apoptosis, establishment of immunological memory, germinal center

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formation in lymphoid tissues, modulation of cytokine production in activated B cells and B cell proliferation and differentiation

A soluble version of CD40L can be made from the extracellular region or fragments thereof. As used herein, the term CD40L includes soluble CD40L polypeptides lacking transmembrane and intracellular regions, homologs and analogs of CD40L or derivatives thereof. Early studies have shown that CD40L is a member of the tumor necrosis factor (TNF) family of cytokines. Other members of this family include TNF-$\alpha$, LT-$\alpha$ (lymphotoxin-$\alpha$, known also as TNF-$\beta$), LT-$\beta$, Fas ligand, CD30L and CD27L. CD40L is a membrane bound polypeptide with an extracellular region at its C terminus, a transmembrane region, and an intracellular region at the N terminus.

Several mutations of CD40L are known to cause an X-chromosome-linked severe immunodeficiency, known as Hyper-IgM syndrome ("HIGMS"). HIGMS is characterized by normal or elevated levels of IgM, but absent or low levels of IgG, IgA and IgE in serum. A murine CD40L gene "knockout" also lacks expression of IgG, IgA and IgE, similar to Hyper-IgM syndrome in man. These observations suggest that CD40 signaling is required for IgG, IgA, and IgE production, and that this function is non-redundant with other signaling/adhesion pathways. Studies show that CD40L may also play roles in certain diseases such as arthritis, lupus, multiple sclerosis, graft versus host disease, ulcerative colitis, allergies, tissue transplantation and generation of antibodies against antigenic drugs. Thus, it is apparent that interfering with the CD40-CD40L interaction has wide reaching therapeutic and diagnostic applications.

There is presently an interest in designing, identifying or obtaining potential drug candidates which would interfere with the CD40-CD40L interaction. The recent emergence of drug design to identify candidates that play a

role in a physiologically relevant biological pathway has provided a useful approach for obtaining, or designing, lead compounds for drugs.

Generally, this approach requires selecting a protein target molecule which plays a role in a physiologically relevant biological pathway. Typically, once a ligand, natural or synthesized, is found for the target molecule, it is modified or optimized to produce a candidate with the desired properties.

In order to more efficiently design or modify a ligand, it is useful to have a three-dimensional structure for the bioactive conformation of a known ligand as it binds to the target protein molecule. Furthermore, it is valuable to understand the detailed interactions of the ligand with its target protein by examining the three-dimensional structure of the protein target in complex with its known ligand. This allows the artisan to preserve the critical interactions with the protein, while modifying candidate ligands to interact more precisely with the protein, resulting in better potency and specificity.

However, the three dimensional crystal structure of the protein target is frequently unavailable due to the significant effort required to obtain crystals of sufficient size and resolution to provide accurate information regarding the structure. For example, it is time consuming and often difficult to express, purify and characterize a protein. Additionally, once the protein of sufficient purity is obtained, it must be crystallized to a size and clarity which is useful for x-ray diffraction and subsequent structure solution. Thus, although crystal structures can provide a wealth of valuable information in the field of drug design and discovery, crystals of certain biologically relevant compounds such as CD40L, are not readily available to those skilled in the art.

Furthermore, although the amino acid sequence of a

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target protein or its ligand, such as CD40L, is known, this
sequence information does not allow an accurate prediction
of the crystal structure of the protein/ligand. Nor does
the sequence information afford an understanding of the
structural, conformational and chemical interactions between
a ligand such as CD40L and its protein target.

Thus, there is a need for a detailed knowledge of the
crystalline three-dimensional structure of the extracellular
domain of CD40L, to effectively design, screen or optimize
compounds capable of interfering with the CD40L -CD40
interactions. Although the binding of CD40 and its ligands
has been studied, and similarities found between this system
and the TNF system, the differences that exist suggest that
these two ligand-receptor systems utilize spatially
overlapping, but nonidentical and nonconserved sites of
contact residues with different molecular determinants of
binding.

Crystals of CD40L or fragments of CD40L of a size and
quality such as to allow performance of x-ray diffraction
studies would enable those skilled in the art to conduct
studies relating to the binding properties of CD40L, as well
as the binding properties of molecules or molecular
complexes which may associate with CD40L or a fragment
thereof.

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## SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to

5    crystals of CD40L or crystals of fragments of CD40L, of
sufficient size and quality to obtain useful information
about the properties of CD40L and molecules or complexes
which may associate with CD40L or CD40.  The claimed
invention provides the three-dimensional crystal structure

10   of the Gly116 to Leu261 fragment of CD40L, which can be used
to identify binding sites to solve the structure of unknown
crystals, to provide mutants having desirable binding
properties, and ultimately, to design, characterize, or
identify molecules or chemical entities capable of

15   interfering with the interaction between CD40 and CD40L.

Additional features and advantages of the invention
will be set forth in the description which follows, and in
part will be apparent from the description, or may be
learned by practice of the invention.  The objectives and

20   other advantages of the invention will be realized and
attained by the compositions and methods particularly
pointed out in the written description and claims hereof, as
well as in the appended drawings.

To achieve these and other advantages, and in

25   accordance with the purpose of the invention, as embodied
and broadly described herein, the invention relates to a
crystal of CD40L.  More particularly, the invention relates
to a crystal formed by a functional fragment of the
extracellular domain of sCD40L(116-261), wherein the crystal

30   has cell constants a=b=77.17Å, c= 90.46Å, $\alpha = \beta = 90°$, $\gamma = $
120°, and a space group of R3, and equivalents of that
crystal.  The claimed crystals of CD40L are substantially
described by the structural coordinates identified in Table
1.  The claimed crystals in certain embodiments are

35   characterized by a binding site moiety comprising Ile127,

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Ser128, Glu129, Ala130, Ser131, Thr135, Ser136, Ala141,
Glu142, Lys143, Gly144, Tyr145, Tyr146, Cys178, Asn180,
Ser185, Gln186, Ala187, Pro188, Ile190, Ala191, Ser192,
Ser197, Pro198, Gly199, Arg200, Phe201, Glu202, Arg203,
Ile204, Arg207, Ala209, Thr211, Pro217, Cys218, Gly219,
Gln220, Glu230, Leu231, Gln232, Asn240, Val241, Thr242,
Asp243, Ser245, Val247, Ser248, His249, Gly250, Thr251,
Gly252 and Phe253.

Additionally, the invention relates to crystals of
molecules having a binding site comprising at least Arg207,
and preferably, amino acids Lys143, Arg203, Arg207 and
Tyr145. The claimed crystals in certain embodiments, are
formed from molecules having a binding site moiety
comprising Arg207 surrounded by at least two hydrophobic
residues. Mutants, homologs, co-complexes and fragments of
the claimed crystals are also contemplated herein.

The claimed invention in certain embodiments relates to
heavy atom derivatives of the crystallized form of a
sCD40L(116-261), and, more specifically, the heavy atom
derivatives of the crystallized form of CD40L described
above.    In various embodiments, the claimed invention
relates to methods of preparing crystalline forms of CD40L,
or fragments thereof, by providing an aqueous solution
comprising at least a fragment of CD40L, providing a
reservoir solution comprising a precipitating agent, mixing
a volume of the CD40L solution with a volume of the
reservoir solution and crystallizing the resultant mixed
volume.  In certain embodiments, the crystal is derived from
an aqueous solution comprising sCD40L(116-261). In various
embodiments, the concentration of CD40L in the aqueous
solution is about 1 to about 50 mg/ml, preferably about 5
mg/ml to about 15 mg/ml, and most preferably, about 10
mg/ml. The precipitating agents used in the invention may
be any precipitating agent known in the art, preferably one
selected from the group consisting of sodium citrate,

ammonium sulfate and polyethylene glycol. Any concentration of precipitating agent may be used in the reservoir solution, however it is preferred that the concentration be about 1.0 M to about 1.5 M, more preferably about 1.2 M. Similarly, the pH of the reservoir solution may be varied, preferably between about 4 to about 10, most preferably about 7.5.

Various methods of crystallization can be used in the claimed invention, including, but not limited to, vapor diffusion, batch, liquid bridge, or dialysis. Vapor diffusion crystallization is preferred.

Additionally, the claimed invention relates to methods of using the claimed crystal, and the structure coordinates in methods for screening, designing, or optimizing molecules or other chemical entities that may interfere with the interaction between CD40 and CD40L. Thus, the structural coordinates of CD40L or portions thereof can be used to solve the crystal structure of a mutant, homologue or co-complex of CD40L or a fragment thereof, as well as to solve other unknown crystals which asociate with CD40L or fragments thereof.

In some embodiments, the structural coordinates of the CD40L can be used to evaluate a chemical entity to obtain information about the binding of the chemical entity to CD40L. The claimed invention also relates to the structural coordinates described in Table 1. The structural coordinates can be used to characterize chemical entities which interfere with the relationship between CD40 or CD40L such as inhibitors or agonists. The coordinates can also be used to optimize binding characteristics, to determine the orientation of ligands in the binding site of CD40L or CD40. One skilled in the art will appreciate the numerous uses of the claimed invention in the areas of drug design, screening and optimization of drug candidates, as well as in determining additional unknown crystal structures.

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In various embodiments, the claimed invention relates
to a machine readable data storage medium having a data
storage material encoded with machine readable data, which,
when read by an appropriate machine, can display a three
5    dimensional representation of a crystal.  The crystals
displayed comprise a fragment of CD40L such as that
described by the coordinates in Table 1, or a crystal having
a binding site comprising amino acids Lys143, Arg203, Arg207
and Tyr145.

10       In other embodiments, the claimed invention relates to
a method for determining a at least a portion of a three
dimensional structure of a chemical entity or molecular
complex by calculating phases from the structural
coordinates of a crystal of a fragment of CD40 ligand,
15   calculating the electron density map from the phases
obtained, and then determining at least a portion of the
unknown structure based upon the electron density map.

In yet other embodiments, the invention relates to
methods for evaluating the ability of a chemical entity to
20   associate with CD40 or CD40L.  The methods employ
computational or experimental means to perform a fitting
operation between the chemical entity and the CD40 or CD40L
to obtain data related to the association, and analyzing the
data to determine the characteristics.  Chemical entities
25   identified by these methods which are capable of interfering
with the in vivo or in vitro association between CD40 and
CD40 L are also encompassed by the claimed invention.  The
claimed chemical entities may comprise binding sites
substantially similar to those of CD40L, or, alternatively
30   may comprise binding sites capable of associating with the
binding sites of CD40L.

It is to be understood that both the foregoing general
description and the following detailed description are
exemplary and explanatory and are intended to provide
35   further explanation of the invention as claimed.

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The accompanying drawings are included to provide a
further understanding of the invention and are incorporated
in and constitute a part of this specification, illustrate
several embodiments of the invention, and together with the
5    description, serve to explain the principles of the
invention.

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## BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a depiction of the representative regions of a $2F_o-F_c$ electron density map contoured at $2.5\sigma$ showing residues in the vicinity of the CD40 binding site.

Figure 2 is an electron density map showing a view of a network of 3 tyrosine and 3 histidine residues formed in the vicinity of the center of the trimer of CD40.

Figure 3 is a stereo drawing of the 3-dimensional structure of human CD40L specifically, CD40L $C\alpha$ backbone.

Figure 4 is a ribbon representation and secondary structure assignment of CD40L.

Figure 5 is a sequence alignment of the TNF-like domains of $TNF\alpha$, $Lt\alpha$ and CD40L based on structural considerations.

Figure 6 is a graph of temperature factors of main chain atoms as a function of residue number. Residues are numbered with Pro120 as residue 1.

Figure 7 is a depiction of residues involved in Hyper-IgM and designed mutations. The third monomer has been removed for clarity.

Figure 8 is a summary of sCD40L(116-261) crystallographic and refinement data.

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## DETAILED DESCRIPTION OF THE INVENTION

In order that the invention described herein may be more fully understood, the following detailed description is set forth.

The present invention relates to a crystal of a soluble fragment of the extracellular domain of the CD40 ligand. Specifically, it relates to a crystal of a protein comprising the sequence from Gly116 to Leu261 (sCD40L(116-261)), the structure of sCD40L(116-261) as determined by X-ray crystallography, and the use of the sCD40L(116-261) structure and that of its homologs, mutants and co-complexes to design, identify, characterize, screen and/or optimize candidate inhibitors or agonists of CD40L activity.

## A.   DEFINITIONS

The term CD40 ligand ("CD40L") as used herein refers to a genus of polypeptides which are capable of binding to CD40, or homologs or fragments thereof.  The term as used herein includes sCD40L(116-261), homologs, mutants, equivalents and fragments thereof.

The term "co-complex" refers to a CD40L or a mutant or homolog of CD40L in covalent or non-covalent association with a chemical entity.

The term "homolog" refers to a protein having at least about 50% amino acid sequence identity with the protein to which it is being compared.

The term "mutant" refers to a CD40L or fragment thereof, characterized by the replacement, deletion, or insertion of at least one amino acid from the wild-type. Such a mutant may be prepared, for example, by expression of a CD40L previously altered in its coding sequence by oligonucleotide-directed mutagenesis.

The term " positively charged amino acid" includes any amino acid, natural or unnatural, having a positively charged side chain under normal physiological conditions.

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Examples of positively charged naturally occurring amino acids are arginine, lysine and histidine.

The term "negatively charged amino acid" includes any amino acid, natural or unnatural, having a negatively
5    charged side chain under normal physiological conditions. Examples of negatively charged naturally occurring amino acids are aspartic acid and glutamic acid.

The term "hydrophobic amino acid" means any amino acid having an uncharged, nonpolar side chain that is relatively
10   insoluble in water. Examples are alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophane and methionine.

The term "hydrophilic amino acid" means any amino acid having an uncharged, polar side chain that is relatively
15   soluble in water. Examples are serine, threonine, tyrosine, asparagine, glutamine, and cysteine.

The term "altered surface charge" means a change in one or more of the charge units of a mutant polypeptide, at physiological pH, as compared to CD40 ligand. The change in
20   surface charge can be determined by measuring the isoelectric point (pI) of the polypeptide molecule containing the substituted amino acid and comparing it to the pI of the wild-type molecule.

The term "associating with" refers to a condition of
25   proximity between two chemical entities, or portions thereof, for example, a CD40 ligand or portions thereof and a chemical entity. The association may be non-covalent, wherein the juxtaposition is energetically favored by hydrogen bonding, van der Waals interaction, or
30   electrostatic interaction, or it may be a covalent association.

The term "binding site" refers to any or all of the sites where a chemical entity binds or associates with another entity.

35      The term "structural coordinates" refers to the

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coordinates derived from mathematical equations related to
the patterns obtained on diffraction of a monochromatic beam
of X-rays by the atoms (scattering centers) of molecule in
crystal form.  The diffraction data are used to calculate an
electron density map of the repeating units of the crystal.
Those skilled in the art will understand that the data
obtained are dependent upon the particular system used, and
hence, different coordinates may in fact describe the same
crystal if such coordinates define substantially the same
relationship as those described herein.  The electron
density maps are used to establish the positions of the
individual atoms within the unit cell of the crystal.

Those of skill in the art understand that a set of
structural coordinates determined by X-ray crystallography
is not without standard error.  Table 1 is the atomic
coordinates of sCD40L(116-261).  For the purpose of this
invention, any set of structural coordinates of CD40L(116-
261) that have a root mean square deviation of equivalent
protein backbone atoms of less than about 2 Å when
superimposed--- using backbone atoms-- on the structural
coordinates in Table 1 shall be considered identical.
Preferably the deviation is less than about 1Å and more
preferably less than about 0.5Å.

The term "heavy atom derivatization" refers to a method
of producing a chemically modified form of a crystallized
CD40 ligand.  In practice, a crystal is soaked in a solution
containing heavy metal atom salts, or organometallic
compounds, e.g., lead chloride, gold thiomalate, thimerosal
or uranyl acetate, which can diffuse through the crystal and
bind to the surface of the protein.  The location of the
bound heavy metal atom(s) can be determined by X-ray
diffraction analysis of the soaked crystal.  This
information can be used to generate the phase information
used to construct the three-dimensional structure of the
molecule.

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The term "unit cell" refers to a basic shaped block. The entire volume of a crystal may be constructed by regular assembly of such blocks. Each unit cell comprises a complete representation of the unit of pattern, the repetition of which builds up the crystal.

The term "space group" refers to the arrangement of symmetry elements of a crystal.

The term "molecular replacement" refers to a method that involves generating a preliminary structural model of a crystal whose structural coordinates are unknown, by orienting and positioning a molecule whose structural coordinates are known e.g. the CD40 ligand coordinates in Table 1, within the unit cell of the unknown crystal, so as to best account for the observed diffraction pattern of the unknown crystal. Phases can then be calculated from this model, and combined with the observed amplitudes to give an approximate Fourier synthesis of the structure whose coordinates are unknown. This in turn can be subject to any of the several forms of refinement to provide a final accurate structure of the unknown crystal. (See, e.g., Lattman, E., "Use of the Rotation and Translation Functions", Methods in Enzymology, 115, pp. 55-77 (1985); Rossman, ed., "The Molecular Replacement Method", Int. Sci. Rev. Ser. No. 13, Gordon and Breach, New York (1972). Specifically incorporated by reference herein.) Using the structural coordinates of CD40 ligand provided by this invention, molecular replacement may be used to determine the structural coordinates of a crystalline co-complex, unknown ligand, mutant, homolog, or of a different crystalline form of CD40 ligand. Additionally, the claimed crystal and its coordinates may be used to determine the structural coordinates of a chemical entity which associates with CD40L or CD40.

The term "chemical entity" as used herein shall mean, for example, any molecule, molecular complex, compound or

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fragment thereof.

CD40L mutants may be generated by site-specific incorporation of natural or unnatural amino acids into CD40L using general biosynthetic methods known to those skilled in
5    the art. For example, the codon encoding the amino acid of interest in wild-type CD40L may be replaced by a "blank" nonsense codon, such as TAG, using oligonucleotide-directed mutagenesis. A suppressor tRNA directed against this codon can then be chemically aminoacylated in vitro with the
10   desired amino acid. The aminoacylated tRNA can then be added to an in vitro translation system to yield a mutant sCD40L with the site-specific incorporated amino acid.

The term soluble fragment of CD40L and any equivalent term used herein, refers to a functional fragment of CD40L.
15   The term "functional" as used in this context refers to a soluble fragment of the extracellular domain that is capable of binding to, or associating with, a CD40, CD40-Ig fusion protein or any fragments or homologs thereof, including molecular complexes comprising fragments thereof. Such
20   binding may be demonstrated through immunoprecipitation experiments, using standard protocols known in the art.


A.   CD40L, its Crystal, and its Biological Implications


25        It will be understood that throughout the specification and claims, the positional location of the amino acids described is not an absolute value, but rather, defines the relative relationship of the residues. Thus it is intended that the present invention encompass the sequences having
30   the same or similar relative positions.

For the first time, the present invention permits the use of molecular design techniques to design, screen and optimize chemical entities and compounds, including inhibitory compounds, capable of binding to the active site
35   or accessory binding site of CD40L, in whole or in part.

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CD40 ligand (CD40L) is a T cell membrane-bound pleiotropic
cytokine of considerable biomedical interest because of its
involvement in important immune system functions mediated by
the binding of CD40L to CD40. CD40 is a molecule expressed
on the surface of B cells and other cell types. CD40L is
found in various organisms, such as humans, mice, rats,
pigs, etc. The claimed invention is not intended to be
limited to any particular species or organism.

CD40L is a member of the tumor necrosis factor family
of ligands. The crystal structure of another member of this
family, lymphotoxin-$\alpha$ (LT$\alpha$) complexed with its receptor has
been described and has be used as a framework for
understanding the CD40L crystal structure. However, despite
certain similarities, the differences between the LT system
and the CD40 system confirm that the two ligand-receptor
systems utilize spatially overlapping, but nonidentical and
nonconserved sites of contact residues with different
molecular determinants of binding.

Considering the complexity and overlap of the various
immune system processes, the fact that CD40 signaling
appears to be non-redundant suggests that inhibiting CD40L
signaling may have important therapeutic applications. The
crystal structure of CD40L presented here is expected to be
useful in the design, identification, characterization and
optimization of such therapeutic agents.

The following detailed description of applicants
invention encompasses the (a) crystal structure of
CD40L(116-261) and the coordinates thereof, (b) the binding
sites of CD40L, (c) methods of making a CD40L crystal, and
(d) methods of using the CD40L crystal and its structural
coordinates.

(a.)   Crystal Structure of CD40 Ligand

The claimed invention provides crystals of CD40 ligand,
as well as the structure of CD40 ligand determined
therefrom. Specifically, the claimed invention provides

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crystals of a fragment of CD40 ligand(116-261) having unit
cells which are rhombohedral, and having the following
dimensions a=b=77.17 Å and c=90. 46 Å, $\alpha=\beta=$ 90 Å and $\gamma =$
120 Å.  Almost all of the residues of CD40 ligand fragment,

5    except for residues 116-119 of the N terminus, are well
defined in the final electron density map shown in Figure 1.
There are areas of weak density for residues 182-186 and
210-220.  The current model consists of 142 amino acid
residues and 95 water molecules with a crystallographic R

10   factor of 21.8 % and an $R_{free}$ of 29.1% for data between 7.5 Å
and 2 Å.  The Ramachandran diagram shows that 140 out of
the 142 amino acid residues have $(\phi,\psi)$ angles within the
allowed regions.  The exceptions are residue Cys218, which
is involved in the formation of a disulfide bridge, and

15   Lys143.

         CD40 ligand folds as a sandwich of two β sheets with
jellyroll or Greek key topology (Figure 3).  The dimensions
of the molecule are 25 Å x 30 Å x 50 Å.  The overall fold
is similar to that of TNF-α and LT-α.   The notation used

20   herein is that described in Eck et.al., "The Structure of
Human Lymphotoxin", <u>J. Biol. Chem.</u>, 267, 2119-2112, for the
β strands and other structural features.  One β sheet
consists of strands A"AHCF, and the other of strands B'BGDE.
To assess the degree of structural similarity between TNF-α,

25   LT-α and CD40 ligand, the sequences were aligned to maximize
the overlap of equivalent β strand residues.  The equivalent
Cα atoms from the β strands were then used to superimpose
the molecular structures.  The root mean square (rms)
positional deviation of 86 equivalent Cα atoms of

30   superimposed TNF-α and CD40L molecules is 1.10 Å.  In the
case of the LT/CD40L pair, the rms deviation for the 100
equivalent Cα atoms is 1.03 Å.  The positions of the
residues are highly conserved in the core and β strand
regions, but differ significantly in certain loops, such as

35   the AA", CD and EF loops.  An alignment of the TNF-α, LT-α

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and CD40L sequences based on the best structural
superimpositions was made. Figure 5. Most residues of the
hydrophobic core of CD40L maintain the identity of the
character encountered in the equivalent residues of TNF and
5      LT. There are local compensatory, conformational changes to
accommodate side-chain changes, such as the substitution of
Leu33 of LT-α to Val36 in CD40L, which results in a shift of
the side chain of Leu161 to fill the empty space.

         Three CD40L molecules form a trimer similar to that
10     observed in the crystal structures of TNF-α and LT-α. The
trimer has the shape of a truncated pyramid. The three-
fold axis of the trimer is approximately parallel to the β
strands of each subunit. The interface between the subunits
is formed mainly by two tyrosines, two histidines and one
15     leucine. Thus the "aromatic tiling" observed in LT is not
as prevalent in CD40L. Tyr170 and His224 from each monomer
form an unusual cluster of two triads along the threefold
axis of the trimer.

         The crystal packing of CD40L trimers was also studied.
20     Each CD40L monomer forms one crystal contact that involves
loops DE (residues 198-201), FG (232-233) and BC (64-166)
from one molecule and loops CD (182-186), AA" (131-135) and
GH (245-246) from the neighboring molecule. Sixteen water
molecules are involved in the formation of the contact.

25           The CD and EF loops of CD40L at the "top" of the
molecule are shorter than those of TNF-α and LT-α. However,
despite its shorter length, the CD loop contains 1.5 turns
of a helix in a similar manner to the equivalent loop in LT.
Analogs to LT regions of poor electron density occur within
30     these loops that may indicate disorder. In addition, a plot
of temperature factors (Figure 6) suggests that the CD and
EF loops are the most mobile parts of the molecule. The C
and F strands are linked by a disulfide bridge between
Cys178 and Cys218 that may play a role in stabilizing the
35     top of the molecule. A disulfide bridge is also present in

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TNF but it is located at a different position.  Although the
AA" loop does not differ much between TNF and LT, in CD40L
it has a very different structure.  In CD40L the AA" loop is
shifted away from the CD40L binding site relative to TNF and
LT.  The unusual conformation of the AA" loop may be related
to its extensive participation in the crystal contact.  A
short 10 helical structure is found within the GH loop, and
β bulge occurs in the middle of strand E.  The N and C
terminii lie close to each other at the base of the trimer.
Residues 116-119 of the N terminus of the construct are
poorly defined in the electron-density map, therefore, the
first well ordered residue is Pro120.  Residues 116-119
presumably constitute part of the stalk connecting the
globular domain to the transmembrane segment.  This 65-
residue stalk is unusually long compared with the equivalent
segments in other members of the TNF family.

        A single glycosylation site is predicted from analysis
of the CD40L sequence.  Biochemical experiments revealed
that residue Asn240 of the CD40L protein used for the
crystallization has an N-linked carbohydrate attached to it.
A 2F-Fc map shows electron density in the vicinity of the
side chain of Asn240 which presumably corresponds to the
attached carbohydrate.  However, because the density is not
well defined, the current model contains no carbohydrate
atoms at this position.

        (b.)  Binding Site

        By analogy with the LT-TNFR complex crystal structure,
the CD40 binding site consists of a shallow groove formed
between two monomers.  The activation complex of CD40L-CD40
is expected to be similar to the LT-TNFR complex.  On the
basis of linkage diagrams showing which residue of LT
interacts with which residue of TNFR, stretches of the CD40L
sequence that were likely to constitute the binding site of
CD40L were inferred.

        Applicants have determined that the CD40L binding site

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comprises Arg207 in close physical proximity to at least two
hydrophobic residues. More specifically, the binding sit
comprises at least amino acids Lys143, Arg203, Arg207 and
Tyr145. Numerous other residues may be included in the
5      binding site, including, but not limited to, Ile127, Ser128,
Glu129, Ala130, Ser131, Thr135, Ser136, Ala141, Glu142,
Lys143, Gly144, Tyr145, Tyr146, Cys178, Asn180, Ser185,
Gln186, Ala187, Pro188, Ile190, Ala191, Ser192, Ser197,
Pro198, Gly199, Arg200, Phe201, Glu202, Arg203, Ile204,
10     Arg207, Ala209, Thr211, Pro217, Cys218, Gly219, Gln220,
Glu230, Leu231, Gln232, Asn240, Val241, Thr242, Asp243,
Ser245, Val247, Ser248, His249, Gly250, Thr251, Gly252 and
Phe253.

One skilled in the art will appreciate that
15     modifications to the binding site, i.e. substitutions,
insertions or deletions, may be made and the binding site
will maintain its activity. Thus, it is contemplated that a
binding site comprising at least 50 % homology to that
defined above is encompassed by the invention. More
20     specifically, it is preferred to have about 60% homology,
and most preferred about 75-99% homology. Variations in the
percentage of homology to the binding site defined above may
alter the binding properties of the resultant entity. In a
preferred embodiment, the binding site comprises at least 30
25     residues from the list defined above.

The binding site was expected to contain residues
mostly from the AA" and DE loops. In addition, residues
from the CD and GH loops and B strands, C, D, G and H were
expected to be involved in CD40 binding. Virtually no
30     sequence conservation exists between CD40L and LT-α or TNF-α
in these regions. Although Ser131 of the AA" loop appears
to be conserved in the sequence alignment, the structural
superimposition shows that it is relatively distant from the
equivalent position (Ser38) in LT. The Tyr45 side chain of
35     the AA" loop of CD40L is disordered, but is found in an

equivalent position at Arg51 of LT, and, like Arg51 in the
LT-α-TNFR complex, may have an extended and well-defined
conformation in the complex. On the DE loop, only Phe201 is
conserved (equivalent to Phe110 of LT). Phe201 adopts a
similar conformation to that of Phe110 in the LT-α-TNFR
complex, whereas in the uncoupled LT, Phe110 adopts a
different conformation. The Arg200 side chain in the DE
loop is involved in a crystal contact. The conformation of
loops DE AA" and GH is likely to be affected by the crystal
contact, thus, it is expected that their structure will be
different in a complex. The conformational changes
associated with complex formation in the case of LT,
although minor, may be indicative of the magnitude of
changes that occur upon CD40 binding to CD40L.

A mixture of both hydrophobic and hydrophilic residues
form the surface of the binding site. The LT-TNFR binding
interface can be considered as separate upper and lower
regions. In a similar manner to LT, the upper region in
CD40L has more hydrophobic and non-charged polar residues
than the lower region. Arg207 is an important residue,
lying in the area where the upper and lower regions connect.
The Arg207 side chain adopts an extended conformation
pointing towards the putative location of the CD40 receptor,
and is surrounded by at least two surface-exposed
hydrophobic residues and a serine residue (Ser192). Two of
the hydrophobic residues (190 and Phe253) belong to the
neighboring subunit, whereas Ile204 is from the same
subunit. Murine CD40L has a lysine in the position
equivalent to that of Arg207 of human CD40L, and this lysine
also seems likely to be surrounded by hydrophobic residues.
The hydrophobic environment of the arginine may amplify the
strength of a possible electrostatic interaction between
this residue and an acidic residue of CD40.

(c.)  Methods of Making a CD40L Crystal

In various embodiments, the claimed invention relates

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to methods of preparing crystalline forms of CD40L, or
fragments thereof by first providing an aqueous solution
comprising CD40L or a fragment of CD40L.  A reservoir
solution comprising a precipitating agent is then mixed with
a volume of the CD40L solution and the resultant mixed
volume is then crystallized.  In certain embodiments, the
crystal is derived from an aqueous solution comprising
sCD40L(116-261).  The concentration of CD40L in the aqueous
solution may vary, and is preferably about 1 to about 50
mg/ml, more preferably about 5 mg/ml to about 15 mg/ml, and
most preferably, about 10 mg/ml.  Similarly, precipitating
agents used in the invention may vary, and may be selected
from any precipitating agent known in the art.  Preferably
the precipitating agent is selected from the group
consisting of sodium citrate, ammonium sulfate and
polyethylene glycol.  Any concentration of precipitating
agent may be used in the reservoir solution, however it is
preferred that the concentration be about 1.0 M to about 1.5
M, more preferably about 1.2 M. The pH of the reservoir
solution may also be varied, preferably between about 4 to
about 10, most preferably about 7.5.  One skilled in the art
will understand that each of these parameters can be varied
without undue experimentation and acceptable crystals will
still be obtained.  In practice, once the appropriate
precipitating agents, buffers or other experimental
variables are determined for any given growth method, any of
these methods or any other methods can be used to grow the
claimed crystals.  One skilled in the art can determine the
variables depending upon his particular needs.

        Various methods of crystallization can be used in the
claimed invention, including, but not limited to, vapor
diffusion, batch, liquid bridge, or dialysis.  Vapor
diffusion crystallization is preferred.  See, e.g. McPherson
et al., "Preparation and Analysis of Protein Crystals",
Glick,. Ed., pp 82-159, John Wiley & Co. (1982); Jancarik

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et.al., "Sparse matrix sampling: a screening method for
crystallization of protein", J. Appl. Cryst. 24, 409-411
(1991), specifically incorporated by reference herein.

In vapor diffusion crystallization, a small volume
5    (i.e. a few milliliters) of protein solution is mixed with a
solution containing a precipitating agent.  This mixed
volume is suspended over a well containing a small amount,
i.e. about 1 ml, of precipitating solution.  Vapor diffusion
from the drop to the well will result in crystal formation
10   in the drop.

The dialysis method of crystallization utilizes a
semipermeable size exclusion membrane which retains the
protein but allows small molecules (i.e. buffers and
precipitating agents) to diffuse in and out.  In dialysis,
15   rather than concentrating the protein and the precipitating
agent by evaporation, the precipitating agent is allowed to
slowly diffuse through the membrane and reduce the
solubility of the protein while keeping the protein
concentration fixed.

20   The batch methods generally involve the slow addition
of a precipitating agent to an aqueous solution of protein
until the solution just becomes turbid, at this point the
container can be sealed and left undisturbed for a period of
time until crystallization occurs.

25   Thus, applicants intend that the claimed invention
encompass any and all methods of crystallization.  One
skilled in the art can choose any of such methods and vary
the parameters such that the chosen method results in the
desired crystals.

30   (d.)  Use of CD40L Crystal and its Coordinates
The claimed crystals, and coordinates describing them,
permit the use of molecular design techniques to design,
select and synthesize chemical entities and compounds,
including inhibitory compounds or agonists capable of
35   binding to, or associating with, the binding site of CD40L

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or CD40 in whole or in part.

One approach enabled by this invention is the use of the structural coordinates of CD40L to design chemical entities that bind to or associate with, CD40L and alter the physical properties of the compounds in different ways. Thus, properties such as, for example, solubility, affinity, specificity, potency, on/off rates or other binding characteristics may all be altered and/or optimized.

One may design desired chemical entities by probing a CD40L crystal with a library of different entities to determine optimal sites for interaction between candidate chemical entities and CD40L. For example, high resolution x-ray diffraction data collected from crystals saturated with solvent allows the determination of where each type of solvent molecule sticks. Small molecules that bind tightly to those sites can then be designed and synthesized and tested for the desired activity. Once the desired activity is obtained, the molecules can be further optimized.

The claimed invention also makes it possible to computationally screen small molecule data bases or computationally design chemical entities or compounds that can bind in whole, or in part, to CD40 or CD40L. They may also be used to solve the crystal structure of mutants, co-complexes, or of the crystalline form of any other molecule homologous to, or capable of associating with, at least a portion of CD40L.

One method that may be employed for this purpose is molecular replacement. An unknown crystal structure, which may be any unknown structure, such as, for example, another crystal form of CD40L, a CD40L mutant, or a co-complex with CD40, or any other unknown crystal of a chemical entity which associates with CD40L which is of interest, may be determined using the structural coordinates of this invention, set forth in Table 1. Co-complexes with CD40L may include, but are not limited to, CD40-CD40L, CD40L-small

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molecule, and CD40-derived fragments.  This method will
provide an accurate structural form for the unknown crystal
more quickly and efficiently than attempting to determine
such information without the claimed invention.

5        The information obtained can thus be used to optimize
potential inhibitors or agonists of CD40L, or CD40, and more
importantly, to design and synthesize novel classes of
chemical entities which will affect the relationship between
CD40L and CD40.

10       The design of compounds that inhibit or agonize CD40L
according to this invention generally involves consideration
of at least two factors.  First, the compound must be
capable of physically or structurally associating with CD40L
or CD40.  The association may be any physical, structural,

15 or chemical association, such as, for example, covalent or
noncovalent bonding, van der Waals interactions, hydrophobic
or electrostatic interactions.

      Second, the compound must be able to assume a
conformation that allows it to associate with CD40 or CD40L.

20 Although not all portions of the compound will necessarily
participate in the association with CD40 or CD40L, those
non-participating portions may still influence the overall
conformation of the molecule.  This in turn may have a
significant impact on the desirability of the compound.

25 Such conformational requirements include the overall three-
dimensional structure and orientation of the chemical entity
or compound in relation to all or a portion of the binding
site.

      The potential inhibitory or binding effect of a

30 chemical compound on CD40 or CD40L may be analyzed prior to
its actual synthesis and testing by the use of computer
modeling techniques.  If the theoretical structure of the
given compound suggests insufficient interaction and
association between it and CD40 or CD40L, the need for

35 synthesis and testing of the compound is obviated.  However,

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if computer modeling indicates a strong interaction, the
molecule may then be synthesized and tested for its ability
to bind to CD40 or CD40L.  Thus, expensive and time
consuming synthesis of inoperative compounds may be avoided.

5

An inhibitory or other binding compound of CD40 or
CD40L may be computationally evaluated and designed by means
of a series of steps in which chemical entities or fragments
are screened and selected for their ability to associate
10      with the individual binding sites of CD40L.

Thus, one skilled in the art may use one of several
methods to screen chemical entities or fragments for their
ability to associate with CD40L and more particularly, with
the individual binding sites of sCD40L(116-261).  This
15      process may begin by visual inspection of, for example, the
binding site on a computer screen based on the CD40L
coordinates in Table 1.  Selected fragments or chemical
entities may then be positioned in a variety of
orientations, or "docked", within an individual binding
20      pocket of CD40L.  Docking may be accomplished using software
such as Quanta and Sybyl, followed by energy minimization
and molecular dynamics with standard molecular mechanics
force fields, such as CHARMM and AMBER.

Specialized computer programs may be of use for
25      selecting interesting fragments or chemical entities.
(GRID, available from Oxford University, Oxford, UK; MCSS or
CATALYST, available from Molecular Simulations, Burlington,
MA; AUTODOCK, available from Scripps Research Institute, La
Jolla, CA; DOCK available from University of California, San
30      Francisco, CA., XSITE, University College of London, UK.)

Once suitable chemical entities or fragments have been
selected, they can be assembled into an inhibitor or
agonist.  Assembly may be by visual inspection of the
relationship of the fragments to each other on the three-
35      dimensional image displayed on a computer screen, in

relation to the structural coordinates disclosed herein.

Alternatively, one may design the desired chemical
entities "de novo", experimentally, using either an empty
binding site, or optionally including a portion of a
molecule with desired activity. Thus, for example, one may
use solid phase screening techniques where either CD40L or a
fragment thereof, or candidate chemical entities to be
evaluated are attached to a solid phase thereby identifying
potential binders for further study or optimization.

Basically, any molecular modeling techniques may be
employed in accordance with the invention; these techniques
are known, or readily available to those skilled in the art.
It will be understood that the methods and compositions
disclosed herein can be used to identify, design or
characterize not only entities which will associate or bind
to CD40L, but alternatively to identify, design or
characterize entities which, like CD40L, will bind to CD40
thereby disrupting the CD40L-CD40 interaction. The claimed
invention is intended to encompass these methods and
compositions broadly.

Once a compound has been designed or selected by the
above methods, the efficiency with which that compound may
bind to CD40L may be tested and optimized using
computational or experimental evaluation. Various
parameters can be optimized depending on the desired result.
These include, but are not limited to, specificity,
affinity, on/off rates, hydrophobicity, solubility and other
characteristics readily identifiable by the skilled artisan.

Thus, one may optionally make substitutions, deletions,
or insertions in some of the components of the chemical
entities in order to improve or modify the binding
properties. Generally, initial substitutions are
conservative, i.e the replacement group will have
approximately the same size, shape, hydrophobicity and

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charge as the original component.

The present invention also enables the design of
mutants of CD40L and the solving of their crystal structure.
More particularly, the claimed invention enables one skilled
5      in the art to determine the location of binding sites and
interfaces, thereby identifying desirable sites for
mutation.

For example, mutation may be directed to a particular
site or combination of sites on the CD40L, by replacing or
10     substituting one or more amino acid residues.  Such mutants
may have altered binding properties which may or may not be
desirable.

The mutants may be prepared by any methods known in the
art, such as for example, site directed mutagenesis,
15     deletion or addition, and then tested for any properties of
interest.  For example, mutants may be screened for an
altered charge at a particular pH, tighter binding, better
specificity etc.

The CD40L structure suggests that most, if not all, of
20     the naturally occurring single-site HIGMS mutations affect
the folding and stability of the protein rather than the
binding site directly.  Indeed, more severe HIGMS mutations
involving deletions or other drastic changes would be
expected to perturb the structure much more than single-site
25     mutations.  In addition, only two of the six binding-site
residues selected for mutagenesis were found to be critical
for CD40 binding.

A similar low frequency of hits was found in an
analogous mutational study of LTα.  Van Ostade et al.,
30     "Structure activity studies of human tumour necrosis
factors.", Protein Engineering 7: 5-22 (1994).  This
observation raises the question of whether mutations of
individual CD40L binding-site residues are generally
sufficient to completely disrupt CD40L-CD40 binding.  If
35     insufficient, CD40-mediated cellular signaling will continue

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and the mutation will be clinically undetectable.  This
behavior is consistent with the fact that, in the LTα-
receptor complex structure, as many as 38 LTα residues are
involved in the binding interface.  The interface is quite
5       extensive (520 Å²) and is presumably of similar dimensions
in the CD40L-CD40 complex.  It is expected, therefore, that
each residue only contributes a small fraction of the
binding energy.  However, the interaction of the human
growth hormone with its receptor has also been shown to
10      involve a large surface area, yet relatively few key
residues contribute most of the binding energy.

Additionally, the claimed invention is useful for the
optimization of potential small molecule drug candidates.
Thus, the claimed crystal structures can be also be used to
15      obtain information about the crystal structures of complexes
of the CD40 ligand and small molecule inhibitors.  For
example, if the small molecule inhibitor is co-crystallized
with CD40 ligand, then the crystal structure of the complex
can be solved by molecular replacement using the known
20      coordinates of CD40 ligand for the calculation of phases.
Such information is useful, for example, for determining the
nature of the interaction between the CD40 ligand and the
small molecule inhibitor, and thus, may suggest
modifications which would improve binding characteristics
25      such as affinity, specificity and kinetics.

The detrimental effects of several HIGMS mutations on
CD40L appear to be caused by destabilizing its structure.
For example, Trp140 is a large hydrophobic residue buried
inside the protein and removal of its side chain in the
30      HIGMS mutations Trp140→Gly and Trp140→Arg will obviously
lead to destabilization of the structure.  The valine
affected by the Val126→Ala mutation also participates in
forming the hydrophobic core.  Leu155 is not completely
buried but lies in the middle of β strand B.  Introduction
35      of proline at this position, as in the Leu155→Pro HIGMS

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mutation, may disrupt the formation of the strand.  The
behavior of the HIGMS mutation Ala235→Pro can be similarly
explained.  Substitution of Gly144 in the HIGMS mutation
Gly144→Glu may result in loss of the conformational freedom
5    necessary at that position to form the corner of the AA"
loop.  Consequently, the positioning of the adjacent
residues, Lys143 and Tyr145, which are known to be involved
in binding, is disrupted.  An interesting observation is
that all of the above mentioned residues appear to be
10   clusters:  Trp140, Leu155 and Val126 participate in the
formation of an area of the hydrophobic core partially
formed by strands A, A", B' and B.  Lys143, Gly144 and
Tyr145 are exposed surface residues of the AA" loop lying
very close to the above mentioned hydrophobic residues.
15   This suggests that the CD40-binding capacity is very
sensitive to perturbations in this area of CD40L.

HIGMS mutations Ala123→Glu, Gly227→Val and Thr211→Asp
affect residues that are involved in formation of the
subunit interface.  Ala123 lies near the bottom of the
20   trimer and is within van der Waals distance of three
hydrophobic residues (Leu168, Val228 and Leu261) of the
neighboring subunit.  Gly227 packs against Tyr172 of the
neighboring subunit and Thr211 lies on the EF loop close to
the intersubunit interface where it appears to interact with
25   Arg181 from the neighboring subunit.  Mutations that
introduce larger side chains at these positions (e.g.
Thr211→Asp) would be expected to disturb the intersubunit
packing and possibly prevent trimeritation.  Thus, it
appears that most of the single-site HIGMS mutations affect
30   the folding and stability of CD40L rather than playing a
direct role in CD40 binding.  In addition, mutations of only
two of the nine targeted surface residues appear to affect
CD40 binding.

Mutagenesis studies on CD40L have shown that residues
35   Tyr145 and Lsy143 are directly involved in CD40 binding.

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The crystal structure shows that both residues lie on the
AA″ loop and are surface-exposed. Figure 7. The equivalent
loop in the LT-TNFR crystal structure is involved in several
ligand receptor contacts suggesting similarities in binding.
Tyr145 lies at the corner of the loop and its side chain has
no visible electron density which suggests that it is
disordered. Atom N1 of Lys143 forms a hydrogen bond with
Oδ1 of Glu129. Figure 2. The electron density map also
shows that the side chain of Lys143 has an additional
conformation. Ser128 and Glu129, two residues involved in
the HIGMS mutation Ser128→ArgGlu129→Gly lie close to Lys143
and are well defined in the map. Ser128 is almost
completely buried, and its side-chain hydroxyl group is
within hydrogen bonding distance of His249. It has been
shown that the Glu129-Gly substitute found in the HIGMS
mutation affects a solvent accessible residue that might
participate in binding to CD40. Bajorath et al.,
"Identification of Residues on CD40 and its Ligand which are
Critical for the Receptor-ligand interaction", Biochemistry
34, 1833-1844 (1995), specifically incorporated herein by
reference. One possible candidate for it is the exposed
residue Lys143, and loss of its hydrogen bond to Glu129 may
destabilize its conformation resulting in reduced CD40
binding. All of these residues are conserved in the murine
CD40L sequence.

Five additional single-site mutations, in which
residues Ser131, Asn180, Phe201, Glu202 and Asn240 (located
at the binding site) were substituted by alanine,
established that these residues are not critical for CD40
binding. In addition, two other mutations at residue
positions outside of the binding site (Thr135 and Asp243)
were also shown not to affect binding. According to the
structure, Ser131 and Thr135 lie on the AA″ loop and their
side chains are not exposed. Asn240, the site of
glycosylation, is exposed to the solvent. Because the

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attached sugar would be expected to make Asn240 unavailable
for interaction with CD40, we conclude that it is probably
not involved in CD40 binding, in agreement with the
mutagenesis results.  Asp243 is a semi-exposed residue and
5      it makes a hydrogen bond to Asn186.  Asn180 is an exposed
residue at the top of the molecule.  Its side chain makes
hydrogen bonds to residues 183 and 216.  Phe201 and Glu202
both lie on the DE loop in the binding site area and are
exposed to the solvent.

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C.  EXAMPLES

1.  Determination of Crystal Structure of sCD40L(116-261)

   A.  Crystallization

5        Buffer chemicals were purchased from Fisher (Boston,
MA).  Crystallization condition screenings were done with
the Crystal Screen™ kit from Hampton Research (Riverside,
CA).  A soluble fragment of the extracellular domain of
human CD40 ligand containing amino acid residues Gly116 to
10   the C-terminal residue Leu261 was produced in soluble form
and purified as follows:

         The gene encoding the sCD40L(116-261) sequence of amino
acids G116-L261 was cloned into the Pichia pastoris
expression vector pWS106 and the sCD40L(116-261) protein was
15   expressed by using standard protocols.  Peitsch et al., "A
B-D Model for the CD40 Ligand Predicts That it is a Compact
Trimer Similar to the Tumor Necrosis Factors.", Int.
Immunol. 5, 233-238.  (1993).  pWS106 is a variant of vector
pPIC9 (Invitrogen) with the NcoI site at 3634 nt in the 3'-
20   AOX1 flanking region deleted by site directed mutagenesis.
The cells were lysed and the medium was dialyzed overnight
with 20mM Tris-HCl, pH 6.8 and loaded onto an SP (Pharmacia)
column.  The bound sCD40L was eluted by 2xPBS, pH 7.2 and
buffer-exchanged to 1xPBS.

25       The protein stock was made available as a solution of 8
mg/ml sCD40L in PBS (20.44 g/lt $Na_2HPO_4$, 7.73 g/lt
$Na_2HPO_4$-$H_2O$, 87.66 g/lt NaCl) buffer.  Crystals were grown by
the vapor diffusion method.  (see Jancarik et.al.).  In
order to find conditions of crystallization, an incomplete
30   factorial screen was set up.  In a typical experiment,
protein solution was mixed with an equal volume of reservoir
solution and a drop of the mixture was suspended under a
glass cover slip over the reservoir solution.  Crystals were
grown out of 1.4 M Na Citrate, 50 mM Na, Hepes pH 7.5
35   reservoir solution.  The crystals are shaped as cubes, are

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easy to reproduce and can reach maximum dimensions of almost
1mm on each side (optimal concentration of precipitant to
yield the biggest crystals is 1.2 M Na Citrate). Variation
of pH between 7 and 8 did not affect crystal quality.
Macroseeding techniques were also successful, although not
necessary, to get crystals of sufficient quality for data
collection. Crystal composition was assayed after washing,
dissolution in water and SDS electrophoresis. The gel
showed a strong band of about 20,000 daltons and a much
fainter band of 17,000 daltons. The fainter band
corresponds to non-glycosylated protein while the stronger
band corresponds to the glycosylated form.

Those of skill in the art will appreciate that the
aforesaid crystallization conditions can be varied. By
varying the crystallization conditions, other crystal forms
of sCD40L may be obtained. Such variations may be used
alone or in combination, and include: varying final protein
concentrations between 5 mg/ml and 35 mg/ml; varying the
SCD40L to precipitant ratio; varying citrate concentrations
between 1.2 M and 2.0 nM; varying pH ranges between 5.5 and
9.5; varying HEPES concentrations between 5 and 395 mM;
varying the concentration or type of detergent; varying the
temperature between -5 °C and 30 °C; and crystallizing
SCD40L by batch, liquid bridge, or dialysis method using the
above conditions or variations thereof. See McPherson, A.
(1982). Preparation and Analysis of Protein Crystals.
(Glick, ed.) pp. 82-159, John Wiley & Co., N.Y.,
specifically incorporated by reference herein.

B. Data collection and processing

Crystals were mounted inside capillary tubes and tested
for diffraction capacity on the X-ray beam of an Elliot
GX-13 generator. Oscillation photographs showed strong
diffraction to high resolution. Initial inspection of the
photographs suggested an almost cubic lattice.

A large crystal (0.8 x 0.8 x 0.8 mm) was equilibrated

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gradually in a cryoprotectant solution of 20% glycerol, 1.2
M Na Citrate , 50 mM Na Hepes pH 7.5, mounted on a loop and
immediately frozen in a -150 °C liquid nitrogen gas stream.
The technique of freezing the crystals essentially
5    immortalizes them and produced a much higher quality data
set.  A native X-ray data set up to 1.75 Å resolution was
collected by using a Nicolet/Siemens multiwire area detector
(Siemens, Inc.).  The data were integrated and reduced using
BUDDHA (25) and the CCP4 program package (The SERC (UK)
10   Collaborative Computing Project No 4, Daresbury Laboratory,
UK 1979).  The data collection required about 5 days.

Data processing suggested a rhombohedral unit cell with
approximate cell dimensions a=b=c=55 Å and α=β=γ=91.  To
assist calculations, a hexagonal unit cell is defined
15   instead with dimensions a=b=77.17 Å, c=90.46 Å, γ=120
degrees.  Merging of data suggested that the space group is
R3.  If space group R3 is assumed, then $R_{merge}$ is 6.7%.
Assuming space group R32, $R_{merge}$ is 16.6%.  Table 1 contains
information for the data set obtained.

20   Calculation of the Matthews volume gives VM= 533,610
$A^3/Z*MW$=2.97 assuming Z=9 (#of asymmetric units in unit
cell) and MW=20,000 daltons.  Eck et.al., J. Biol.Chem.
267, 2119-2112 (1992), specifically incorporated herein by
reference.  Thus, it was not clear initially whether there
25   were one or two monomers in the asymmetric unit.

C. Molecular replacement

All subsequent molecular replacement and refinement
computing was done with the XPLOR program package.
Molecular graphics manipulations were done with QUANTA
30   (Molecular Simulations, Inc.) software.  Both XPLOR and
QUANTA were run on a Silicon Graphics Indigo2 computer
workstation.

To investigate whether non-crystallographic symmetry
was present, the self rotation function was calculated with
35   8-4 Å data.  A very strong peak was found for φ=90°, ψ=90°,

κ=180°, which corresponds to the crystallographic 3-fold
axis. This coincides with the 3-fold axis of the trimer of
SCD40L. Also, less strong peaks appeared for φ=0°, ψ=30°,
κ=180° and φ=0°, ψ=90°, κ=180° and φ=0°, ψ=150°, κ=180°

5    corresponding to 2-fold axes perpendicular to the 3-fold.
None of these axes corresponded to non-crystallographic
symmetry.

A 3-dimensional model of the human sCD40L was
constructed by using the murine CD40L model as a framework,

10   using QUANTA protein homology modeling software. The model
was used as a probe for molecular replacement calculations.

Calculation of the cross rotation function by using a
2.5° angle grid and 8-4 Å data produced a strong peak 4.5σ
above the mean, at Euler angles $\theta_1=234.5°$, $\theta_2=5.0°$,

15   $\theta_3=234.5°$. Rotation of the model according to that solution
and subsequent generation of symmetry-related molecules
corresponding to the 3-fold crystallographic symmetry
produces a trimer with the 3-fold axis parallel to the z
axis, as expected. The exact rotation solution was found

20   with Patterson correlation refinement. No significant
second peak was observed in the rotation function.

In order to conduct the translation search, the model
probe was rotated according to the first peak of the
rotation search and translated so that the center of mass of

25   the trimer would lie on the z axis. This was assumed to be
close to the expected position since it appeared that the
3-fold axis of the trimer lay on the z axis of the unit
cell. Initial attempts to find a clear peak in the
translation function on the xy plane failed. Trimmed model

30   probes, which contained mostly core residues whose structure
was more likely to be conserved among different members of
the TNF family, produced translation functions with a
clustering of peaks at locations close to the expected ones.
One of those trimmed models containing all backbone atoms as

35   well as side chain atoms for residues 8-12, 53-62, 90-93,

110-114 and 141-146 produced a peak with a correlation
coefficient of 3.3σ above the mean at x=0.053, y=0.053.
This peak was the highest on the list of peaks and was close
to the expected position.

5          By generating symmetry related molecules and displaying
them with computer graphics it was found that they packed
satisfactorily in the unit cell and that there was not
enough space for a second molecule.  Thus, we concluded
that there was only one molecule in the asymmetric unit.
10  The existence of 2-fold symmetry in the self rotation
function apparently is a consequence of internal symmetry
within the molecule, possibly related to the high content of
parallel strands.  In fact, the self rotation function
calculated from structure factors derived from the model
15  shows peaks corresponding to 2-fold symmetry.

    D. Model building and crystallographic refinement

           The param19.pro stereochemical parameter set of XPLOR
package was used for all refinement calculations.  The
partial model that was used to find the solution of the
20  translation function was subjected to rigid body refinement
by using 7.5-2.5 Å data.  The R and $R_{free}$ (29) factors after
the initial rigid body refinement were 49.9% and 51.4%
respectively.  The test data set used for the calculation of
$R_{free}$ contained 10% of the data.  The partial model was
25  subjected to 40 steps of conventional positional refinement
and a cycle of simulated annealing with an initial
temperature of T=2500 K.  The R and $R_{free}$ factors dropped to
31.2% and 43.1% respectively.  To reduce model bias, a
partial model was used for map calculation  and refinement.
30  The resolution range used was 7.5-2.5 Å.  Simulated
annealing omit maps (30) calculated by consequently omitting
10% of the model each time showed which parts of the model
could be used for phasing.  Thus, the model was modified to
include only residues sufficiently well defined in annealed
35  omit maps.  The initial model included 815 atoms out of a

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total of 1374 atoms of the complete model.  $3F_o -2F_c$  maps
were used for cycles of model building and refinement.
Typically, cycles consisted of model building, positional
refinement and B-factor refinement.  Occasionally simulated
annealing was performed.  As the phases improved, more atoms
were added into the model.  Initially, grouped B-factors
were assigned for each strand (one for main chain and the
one for side chain atoms).  Later, grouped B-factors and
finally individual atomic B-factors where refined for each
residue.  Only manual structure modifications that resulted
in lower $R_{free}$ after refinement were accepted.  When R and
$R_{free}$ reached 31.1% and 36.4% respectively, the resolution
was extended to 2.25 Å and finally to 2 Å.  Water molecules
were added by using the X-solvate utility of QUANTA 4.1.
Both occupancies and temperature factors were refined for
the water molecules.  Figure 8 summarizes information
regarding crystallographic data and refinement.  Table 1
lists the atomic coordinates of sCD40L(116-261).

The coordinates of the crystal structure of a sCD40L
may be used in the structure-based design of small molecule
inhibitors of CD40L, computational drug design and iterative
structure optimization.

a.    Computational drug design

Small molecule inhibitors can be designed using
computational approaches.  These approaches are also known
as de novo drug design.  In brief, the crystal structure
coordinates of the sCD40L are the input for a computer
program, such as DOCK.  Programs such as DOCK output a list
of small molecule structures that are expected to bind to
CD40L.  These molecules can then be screened by biochemical
assays for CD40L binding.

Typically, biochemical assays that screen
molecules for their ability to bind to CD40L are
competition-type assays.  In such assays, the molecule is
added to the assay solution and the degree of inhibition is

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measured using conventional methodology.

    b.    Iterative cycles of structure optimization

        The crystal structures of complexes formed between sCD40L and small molecule inhibitors may be solved. In brief, small molecule inhibitors are typically found using the crystal structure coordinates of a sCD40L either by the computational approaches mentioned above or by the screening of small molecule libraries. The small molecule inhibitor is then co-crystallized with sCD40L and the crystal structure of the complex is solved by molecular replacement. Molecular replacement requires the coordinates of a sCD40L for the calculation of phases. The information collected from these experiments can be used to optimize the structure of small molecule inhibitors by clarifying how small molecules interact with the protein target. This suggests ways of modifying the small molecule to improve its physicochemical properties, such as affinity, specificity, and kinetics with regard to the CD40L target.

        In addition to being necessary for computational drug design and structure optimization, the crystal coordinates of sCD40L are useful for analyzing the CD40L binding site. Through such analysis, it was determined that a particularly attractive region for drug targeting is in the vicinity of Arg207. Arg207 is situated in a region surrounded by three hydrophobic residues and one moderately hydrophobic residue. This grouping appears to demark one wall of a binding groove formed between two CD40L monomers. While not wishing to be bound by theory, it appears that Asp84, or Glu117 of CD40 probably interacts with CD40L at this site. The hydrophobic residues that surround Arg207 may result in increased strength of electrostatic interactions between Arg207, Asp84 and Glu117 of CD40. Specifically, it appears that Glu117 and Asp84 are important. The above observations and hypotheses suggest that this region may contribute significantly to the binding

energy of CD40L/CD40 interactions, and therefore, is an attractive target for inhibitor design. Site mutations studies can be used in conjunction with the above-described processes to further define the binding site.

5          It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the

10    modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents.

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REM'RKS ATOMIC COORDINATES OF CD40L CRYSTAL STRUCTURE IN PDB FORMAT
CRYST    77.170    77.170   90.460   90.00   90.00 120.00 R3
ATOM     1  N    GLY  116     -7.954 -16.144  22.488  1.00 64.71      A
ATOM     2  HT1  GLY  116     -7.087 -15.852  21.964  1.00 15.00      A
ATOM     3  HT2  GLY  116     -8.082 -17.142  22.242  1.00 15.00      A
ATOM     4  HT3  GLY  116     -8.630 -15.576  21.928  1.00 15.00      A
ATOM     5  CA   GLY  116     -7.927 -15.755  23.928  1.00 64.37      A
ATOM     6  C    GLY  116     -6.990 -16.621  24.780  1.00 64.34      A
ATOM     7  O    GLY  116     -6.968 -17.814  24.563  1.00 64.44      A
ATOM     8  N    ASP  117     -6.238 -16.043  25.740  1.00 64.04      A
ATOM     9  H    ASP  117     -5.617 -16.709  26.170  1.00 15.00      A
ATOM    10  CA   ASP  117     -6.284 -14.616  26.130  1.00 63.57      A
ATOM    11  CB   ASP  117     -5.711 -14.402  27.539  1.00 63.36      A
ATOM    12  CG   ASP  117     -6.518 -15.163  28.574  1.00 63.71      A
ATOM    13  OD1  ASP  117     -6.090 -16.247  28.965  1.00 63.24      A
ATOM    14  OD2  ASP  117     -7.566 -14.668  28.987  1.00 63.29      A
ATOM    15  C    ASP  117     -5.651 -13.585  25.184  1.00 63.31      A
ATOM    16  O    ASP  117     -6.039 -12.427  25.145  1.00 63.35      A
ATOM    17  N    GLN  118     -4.713 -14.090  24.379  1.00 62.72      A
ATOM    18  H    GLN  118     -4.450 -15.040  24.541  1.00 15.00      A
ATOM    19  CA   GLN  118     -4.097 -13.313  23.281  1.00 61.79      A
ATOM    20  CB   GLN  118     -2.918 -14.117  22.687  1.00 62.46      A
ATOM    21  CG   GLN  118     -3.047 -15.659  22.562  1.00 62.95      A
ATOM    22  CD   GLN  118     -4.277 -16.118  21.790  1.00 63.26      A
ATOM    23  OE1  GLN  118     -5.396 -16.000  22.277  1.00 63.43      A
ATOM    24  NE2  GLN  118     -4.044 -16.665  20.601  1.00 63.42      A
ATOM    25  HE21 GLN  118     -4.836 -16.715  19.975  1.00 15.00      A
ATOM    26  HE22 GLN  118     -3.151 -16.995  20.298  1.00 15.00     ·A
ATOM    27  C    GLN  118     -4.999 -12.841  22.128  1.00 60.59      A
ATOM    28  O    GLN  118     -4.887 -13.379  21.052  1.00 60.79      A
ATOM    29  N    ASN  119     -5.912 -11.901  22.445  1.00 58.61      A
ATOM    30  H    ASN  119     -5.917 -11.600  23.389  1.00 15.00      A
ATOM    31  CA   ASN  119     -6.689 -11.222  21.386  1.00 56.39      A
ATOM    32  CB   ASN  119     -7.947 -11.982  20.936  1.00 56.95      A
ATOM    33  CG   ASN  119     -7.652 -13.352  20.375  1.00 57.45      A
ATOM    34  OD1  ASN  119     -7.941 -14.303  21.084  1.00 58.50      A
ATOM    35  ND2  ASN  119     -7.005 -13.431  19.241  1.00 58.58      A
ATOM    36  HD21 ASN  119     -6.843 -12.617  18.646  1.00 15.00      A
ATOM    37  HD22 ASN  119     -6.740 -14.221  18.684  1.00 15.00      A
ATOM    38  C    ASN  119     -7.053  -9.724  21.571  1.00 53.62      A
ATOM    39  O    ASN  119     -6.746  -8.933  20.694  1.00 56.55      A
ATOM    40  N    PRO  120     -7.737  -9.288  22.698  1.00 50.17      A
ATOM    41  CD   PRO  120     -8.151 -10.129  23.810  1.00 51.90      A
ATOM    42  CA   PRO  120     -8.402  -7.945  22.818  1.00 48.19      A
ATOM    43  CB   PRO  120     -9.191  -8.008  24.117  1.00 47.42      A
ATOM    44  CG   PRO  120     -9.444  -9.493  24.321  1.00 51.93      A
ATOM    45  C    PRO  120     -7.750  -6.524  22.657  1.00 45.59      A
ATOM    46  O    PRO  120     -8.187  -5.516  23.225  1.00 45.37      A
ATOM    47  N    GLN  121     -6.789  -6.458  21.721  1.00 38.52      A
ATOM    48  H    GLN  121     -6.287  -7.304  21.505  1.00 15.00      A
ATOM    49  CA   GLN  121     -6.733  -5.359  20.753  1.00 29.14      A
ATOM    50  CB   GLN  121     -5.454  -5.735  19.971  1.00 26.30      A
ATOM    51  CG   GLN  121     -5.128  -4.943  18.710  1.00 26.84      A
ATOM    52  CD   GLN  121     -4.923  -3.460  18.949  1.00 27.26      A
ATOM    53  OE1  GLN  121     -5.822  -2.668  18.709  1.00 28.66      A
ATOM    54  NE2  GLN  121     -3.717  -3.100  19.341  1.00 33.90      A
ATOM    55  HE21 GLN  121     -2.883  -3.614  19.564  1.00 15.00      A
ATOM    56  HE22 GLN  121     -3.442  -2.138  19.204  1.00 15.00      A
ATOM    57  C    GLN  121     -8.065  -5.218  19.903  1.00 26.33      A
ATOM    58  O    GLN  121     -8.905  -6.097  19.834  1.00 21.41      A
ATOM    59  N    ILE  122     -8.288  -4.051  19.272  1.00 21.21      A
```

Table 1

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| ATOM | 60 | H | ILE | 122 | -7.600 | -3.320 | 19.337 | 1.00 | 15.00 | A |
|------|----|----|-----|-----|--------|--------|--------|------|-------|---|
| ATOM | 61 | CA | ILE | 122 | -9.383 | -3.952 | 18.295 | 1.00 | 20.92 | A |
| ATOM | 62 | CB | ILE | 122 | -10.238 | -2.629 | 18.396 | 1.00 | 22.17 | A |
| ATOM | 63 | CG2 | ILE | 122 | -11.275 | -2.428 | 17.272 | 1.00 | 21.61 | A |
| ATOM | 64 | CG1 | ILE | 122 | -11.076 | -2.744 | 19.668 | 1.00 | 24.13 | A |
| ATOM | 65 | CD1 | ILE | 122 | -11.751 | -1.440 | 20.073 | 1.00 | 23.04 | A |
| ATOM | 66 | C | ILE | 122 | -8.833 | -4.108 | 16.895 | 1.00 | 18.96 | A |
| ATOM | 67 | O | ILE | 122 | -8.135 | -3.243 | 16.379 | 1.00 | 17.93 | A |
| ATOM | 68 | N | ALA | 123 | -9.159 | -5.240 | 16.283 | 1.00 | 14.72 | A |
| ATOM | 69 | H | ALA | 123 | -9.599 | -5.978 | 16.805 | 1.00 | 15.00 | A |
| ATOM | 70 | CA | ALA | 123 | -8.656 | -5.401 | 14.917 | 1.00 | 14.29 | A |
| ATOM | 71 | CB | ALA | 123 | -7.176 | -5.868 | 14.903 | 1.00 | 12.83 | A |
| ATOM | 72 | C | ALA | 123 | -9.483 | -6.315 | 13.985 | 1.00 | 15.66 | A |
| ATOM | 73 | O | ALA | 123 | -10.170 | -7.261 | 14.323 | 1.00 | 13.58 | A |
| ATOM | 74 | N | ALA | 124 | -9.388 | -6.009 | 12.724 | 1.00 | 13.45 | A |
| ATOM | 75 | H | ALA | 124 | -8.894 | -5.185 | 12.456 | 1.00 | 15.00 | A |
| ATOM | 76 | CA | ALA | 124 | -10.087 | -6.920 | 11.836 | 1.00 | 14.55 | A |
| ATOM | 77 | CB | ALA | 124 | -11.486 | -6.368 | 11.446 | 1.00 | 11.37 | A |
| ATOM | 78 | C | ALA | 124 | -9.271 | -7.123 | 10.563 | 1.00 | 13.54 | A |
| ATOM | 79 | O | ALA | 124 | -8.501 | -6.274 | 10.129 | 1.00 | 16.29 | A |
| ATOM | 80 | N | HIS | 125 | -9.544 | -8.248 | 9.937 | 1.00 | 11.49 | A |
| ATOM | 81 | H | HIS | 125 | -10.100 | -8.900 | 10.426 | 1.00 | 15.00 | A |
| ATOM | 82 | CA | HIS | 125 | -9.100 | -8.524 | 8.590 | 1.00 | 11.51 | A |
| ATOM | 83 | CB | HIS | 125 | -7.605 | -8.908 | 8.614 | 1.00 | 11.43 | A |
| ATOM | 84 | CG | HIS | 125 | -7.119 | -9.116 | 7.205 | 1.00 | 7.41 | A |
| ATOM | 85 | ND1 | HIS | 125 | -6.750 | -8.130 | 6.421 | 1.00 | 6.60 | A |
| ATOM | 86 | HD1 | HIS | 125 | -6.708 | -7.168 | 6.621 | 1.00 | 15.00 | A |
| ATOM | 87 | CD2 | HIS | 125 | -7.075 | -10.291 | 6.456 | 1.00 | 12.36 | ·A |
| ATOM | 88 | NE2 | HIS | 125 | -6.670 | -9.971 | 5.234 | 1.00 | 6.20 | A |
| ATOM | 89 | CE1 | HIS | 125 | -6.462 | -8.646 | 5.211 | 1.00 | 4.48 | A |
| ATOM | 90 | C | HIS | 125 | -10.024 | -9.570 | 7.931 | 1.00 | 12.63 | A |
| ATOM | 91 | O | HIS | 125 | -10.324 | -10.650 | 8.383 | 1.00 | 13.14 | A |
| ATOM | 92 | N | VAL | 126 | -10.550 | -9.129 | 6.806 | 1.00 | 15.65 | A |
| ATOM | 93 | H | VAL | 126 | -10.169 | -8.286 | 6.428 | 1.00 | 15.00 | A |
| ATOM | 94 | CA | VAL | 126 | -11.743 | -9.717 | 6.201 | 1.00 | 14.38 | A |
| ATOM | 95 | CB | VAL | 126 | -12.877 | -8.808 | 6.675 | 1.00 | 13.37 | A |
| ATOM | 96 | CG1 | VAL | 126 | -13.794 | -9.722 | 7.379 | 1.00 | 12.60 | A |
| ATOM | 97 | CG2 | VAL | 126 | -13.449 | -7.663 | 5.814 | 1.00 | 9.61 | A |
| ATOM | 98 | C | VAL | 126 | -11.502 | -9.971 | 4.685 | 1.00 | 16.03 | A |
| ATOM | 99 | O | VAL | 126 | -10.684 | -9.297 | 4.074 | 1.00 | 16.42 | A |
| ATOM | 100 | N | ILE | 127 | -12.118 | -11.013 | 4.136 | 1.00 | 15.99 | A |
| ATOM | 101 | H | ILE | 127 | -12.807 | -11.481 | 4.691 | 1.00 | 15.00 | A |
| ATOM | 102 | CA | ILE | 127 | -11.651 | -11.532 | 2.831 | 1.00 | 14.86 | A |
| ATOM | 103 | CB | ILE | 127 | -11.414 | -13.051 | 3.002 | 1.00 | 17.56 | A |
| ATOM | 104 | CG2 | ILE | 127 | -11.716 | -13.910 | 1.765 | 1.00 | 17.17 | A |
| ATOM | 105 | CG1 | ILE | 127 | -9.972 | -13.316 | 3.399 | 1.00 | 16.47 | A |
| ATOM | 106 | CD1 | ILE | 127 | -9.705 | -12.992 | 4.864 | 1.00 | 19.64 | A |
| ATOM | 107 | C | ILE | 127 | -12.691 | -11.269 | 1.765 | 1.00 | 18.96 | A |
| ATOM | 108 | O | ILE | 127 | -13.898 | -11.391 | 2.016 | 1.00 | 20.01 | A |
| ATOM | 109 | N | SER | 128 | -12.229 | -10.882 | 0.581 | 1.00 | 17.54 | A |
| ATOM | 110 | H | SER | 128 | -11.232 | -10.871 | 0.382 | 1.00 | 15.00 | A |
| ATOM | 111 | CA | SER | 128 | -13.274 | -10.667 | -0.437 | 1.00 | 15.55 | A |
| ATOM | 112 | CB | SER | 128 | -12.664 | -10.130 | -1.706 | 1.00 | 18.16 | A |
| ATOM | 113 | OG | SER | 128 | -12.205 | -11.207 | -2.574 | 1.00 | 19.90 | A |
| ATOM | 114 | HG | SER | 128 | -11.832 | -11.931 | -2.029 | 1.00 | 15.00 | A |
| ATOM | 115 | C | SER | 128 | -14.295 | -11.761 | -0.792 | 1.00 | 13.62 | A |
| ATOM | 116 | O | SER | 128 | -14.052 | -12.960 | -0.832 | 1.00 | 8.98 | A |
| ATOM | 117 | N | GLU | 129 | -15.492 | -11.246 | -1.027 | 1.00 | 13.36 | A |
| ATOM | 118 | H | GLU | 129 | -15.661 | -10.257 | -0.937 | 1.00 | 15.00 | A |
| ATOM | 119 | CA | GLU | 129 | -16.379 | -12.024 | -1.840 | 1.00 | 17.20 | A |

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| ATOM | 120 | CB | GLU | 129 | -17.052 | -13.117 | -1.021 | 1.00 | 20.55 | A |
|------|-----|-----|-----|-----|---------|---------|--------|------|-------|---|
| ATOM | 121 | CG | GLU | 129 | -18.092 | -12.694 | -0.036 | 1.00 | 17.92 | A |
| ATOM | 122 | CD | GLU | 129 | -18.781 | -13.951 | 0.376 | 1.00 | 21.98 | A |
| ATOM | 123 | OE1 | GLU | 129 | -19.997 | -13.932 | 0.368 | 1.00 | 32.23 | A |
| ATOM | 124 | OE2 | GLU | 129 | -18.150 | -14.938 | 0.734 | 1.00 | 33.12 | A |
| ATOM | 125 | C | GLU | 129 | -17.371 | -11.409 | -2.809 | 1.00 | 17.71 | A |
| ATOM | 126 | O | GLU | 129 | -17.972 | -10.389 | -2.553 | 1.00 | 21.59 | A |
| ATOM | 127 | N | ALA | 130 | -17.550 | -12.145 | -3.914 | 1.00 | 20.52 | A |
| ATOM | 128 | H | ALA | 130 | -17.136 | -13.057 | -3.923 | 1.00 | 15.00 | A |
| ATOM | 129 | CA | ALA | 130 | -18.379 | -11.649 | -5.019 | 1.00 | 23.36 | A |
| ATOM | 130 | CB | ALA | 130 | -18.424 | -12.633 | -6.208 | 1.00 | 19.66 | A |
| ATOM | 131 | C | ALA | 130 | -19.811 | -11.298 | -4.570 | 1.00 | 26.86 | A |
| ATOM | 132 | O | ALA | 130 | -20.519 | -12.022 | -3.869 | 1.00 | 29.40 | A |
| ATOM | 133 | N | SER | 131 | -20.198 | -10.086 | -4.968 | 1.00 | 21.70 | A |
| ATOM | 134 | H | SER | 131 | -19.515 | -9.481 | -5.410 | 1.00 | 15.00 | A |
| ATOM | 135 | CA | SER | 131 | -21.592 | -9.782 | -4.732 | 1.00 | 20.04 | A |
| ATOM | 136 | CB | SER | 131 | -21.829 | -8.266 | -4.787 | 1.00 | 20.65 | A |
| ATOM | 137 | OG | SER | 131 | -23.182 | -8.001 | -4.435 | 1.00 | 15.24 | A |
| ATOM | 138 | HG | SER | 131 | -23.329 | -7.069 | -4.559 | 1.00 | 15.00 | A |
| ATOM | 139 | C | SER | 131 | -22.546 | -10.501 | -5.668 | 1.00 | 17.15 | A |
| ATOM | 140 | O | SER | 131 | -22.236 | -10.853 | -6.786 | 1.00 | 14.30 | A |
| ATOM | 141 | N | SER | 132 | -23.756 | -10.731 | -5.187 | 1.00 | 20.15 | A |
| ATOM | 142 | H | SER | 132 | -23.967 | -10.586 | -4.209 | 1.00 | 15.00 | A |
| ATOM | 143 | CA | SER | 132 | -24.674 | -11.250 | -6.218 | 1.00 | 21.62 | A |
| ATOM | 144 | CB | SER | 132 | -25.266 | -12.616 | -5.893 | 1.00 | 16.00 | A |
| ATOM | 145 | OG | SER | 132 | -26.203 | -12.324 | -4.894 | 1.00 | 23.84 | A |
| ATOM | 146 | HG | SER | 132 | -26.016 | -12.944 | -4.179 | 1.00 | 15.00 | A |
| ATOM | 147 | C | SER | 132 | -25.727 | -10.268 | -6.671 | 1.00 | 20.07 | A |
| ATOM | 148 | O | SER | 132 | -26.535 | -10.544 | -7.547 | 1.00 | 20.27 | A |
| ATOM | 149 | N | LYS | 133 | -25.606 | -9.063 | -6.118 | 1.00 | 21.87 | A |
| ATOM | 150 | H | LYS | 133 | -24.904 | -8.969 | -5.397 | 1.00 | 15.00 | A |
| ATOM | 151 | CA | LYS | 133 | -26.406 | -7.916 | -6.517 | 1.00 | 19.23 | A |
| ATOM | 152 | CB | LYS | 133 | -27.024 | -7.309 | -5.256 | 1.00 | 23.08 | A |
| ATOM | 153 | CG | LYS | 133 | -27.684 | -8.364 | -4.354 | 1.00 | 21.07 | A |
| ATOM | 154 | CD | LYS | 133 | -29.174 | -8.110 | -4.330 | 1.00 | 27.36 | A |
| ATOM | 155 | CE | LYS | 133 | -29.939 | -7.884 | -5.670 | 1.00 | 30.56 | A |
| ATOM | 156 | NZ | LYS | 133 | -31.323 | -7.515 | -5.345 | 1.00 | 21.56 | A |
| ATOM | 157 | HZ1 | LYS | 133 | -31.862 | -7.351 | -6.218 | 1.00 | 15.00 | A |
| ATOM | 158 | HZ2 | LYS | 133 | -31.753 | -8.299 | -4.811 | 1.00 | 15.00 | A |
| ATOM | 159 | HZ3 | LYS | 133 | -31.333 | -6.654 | -4.760 | 1.00 | 15.00 | A |
| ATOM | 160 | C | LYS | 133 | -25.579 | -6.876 | -7.194 | 1.00 | 20.10 | A |
| ATOM | 161 | O | LYS | 133 | -24.378 | -6.801 | -7.007 | 1.00 | 17.94 | A |
| ATOM | 162 | N | THR | 134 | -26.260 | -6.052 | -7.983 | 1.00 | 22.95 | A |
| ATOM | 163 | H | THR | 134 | -27.275 | -6.130 | -8.036 | 1.00 | 15.00 | A |
| ATOM | 164 | CA | THR | 134 | -25.556 | -4.879 | -8.561 | 1.00 | 27.89 | A |
| ATOM | 165 | CB | THR | 134 | -26.498 | -4.274 | -9.592 | 1.00 | 24.59 | A |
| ATOM | 166 | OG1 | THR | 134 | -26.540 | -5.037 | -10.792 | 1.00 | 24.32 | A |
| ATOM | 167 | HG1 | THR | 134 | -26.232 | -4.411 | -11.456 | 1.00 | 15.00 | A |
| ATOM | 168 | CG2 | THR | 134 | -26.044 | -2.897 | -9.968 | 1.00 | 22.97 | A |
| ATOM | 169 | C | THR | 134 | -24.987 | -3.798 | -7.559 | 1.00 | 32.51 | A |
| ATOM | 170 | O | THR | 134 | -25.658 | -3.461 | -6.603 | 1.00 | 38.43 | A |
| ATOM | 171 | N | THR | 135 | -23.717 | -3.352 | -7.690 | 1.00 | 35.98 | A |
| ATOM | 172 | H | THR | 135 | -23.292 | -3.555 | -8.585 | 1.00 | 15.00 | A |
| ATOM | 173 | CA | THR | 135 | -22.964 | -3.469 | -6.386 | 1.00 | 36.02 | A |
| ATOM | 174 | CB | THR | 135 | -21.575 | -4.276 | -6.534 | 1.00 | 36.01 | A |
| ATOM | 175 | OG1 | THR | 135 | -21.645 | -5.388 | -7.488 | 1.00 | 30.60 | A |
| ATOM | 176 | HG1 | THR | 135 | -22.255 | -6.094 | -7.312 | 1.00 | 15.00 | A |
| ATOM | 177 | CG2 | THR | 135 | -20.866 | -4.776 | -5.264 | 1.00 | 35.55 | A |
| ATOM | 178 | C | THR | 135 | -22.949 | -2.266 | -5.404 | 1.00 | 30.25 | A |
| ATOM | 179 | O | THR | 135 | -23.541 | -2.348 | -4.331 | 1.00 | 28.35 | A |

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| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 180 | N | SER | 136 | -22.294 | -1.146 | -5.776 | 1.00 | 23.29 | A |
| ATOM | 181 | H | SER | 136 | -22.828 | -0.357 | -5.460 | 1.00 | 15.00 | A |
| ATOM | 182 | CA | SER | 136 | -20.857 | -1.051 | -6.143 | 1.00 | 23.04 | A |
| ATOM | 183 | CB | SER | 136 | -20.560 | 0.187 | -6.965 | 1.00 | 21.03 | A |
| ATOM | 184 | OG | SER | 136 | -20.624 | 1.261 | -6.043 | 1.00 | 28.21 | A |
| ATOM | 185 | HG | SER | 136 | -19.815 | 1.793 | -6.008 | 1.00 | 15.00 | A |
| ATOM | 186 | C | SER | 136 | -19.853 | -1.090 | -4.958 | 1.00 | 21.77 | A |
| ATOM | 187 | O | SER | 136 | -18.630 | -1.096 | -5.080 | 1.00 | 21.94 | A |
| ATOM | 188 | N | VAL | 137 | -20.452 | -1.227 | -3.752 | 1.00 | 24.03 | A |
| ATOM | 189 | H | VAL | 137 | -21.440 | -1.063 | -3.705 | 1.00 | 15.00 | A |
| ATOM | 190 | CA | VAL | 137 | -19.699 | -1.632 | -2.570 | 1.00 | 19.65 | A |
| ATOM | 191 | CB | VAL | 137 | -20.218 | -1.010 | -1.248 | 1.00 | 21.14 | A |
| ATOM | 192 | CG1 | VAL | 137 | -20.419 | -1.907 | -0.058 | 1.00 | 18.16 | A |
| ATOM | 193 | CG2 | VAL | 137 | -21.322 | -0.026 | -1.442 | 1.00 | 13.49 | A |
| ATOM | 194 | C | VAL | 137 | -19.370 | -3.116 | -2.473 | 1.00 | 17.15 | A |
| ATOM | 195 | O | VAL | 137 | -20.209 | -3.969 | -2.593 | 1.00 | 16.69 | A |
| ATOM | 196 | N | LEU | 138 | -18.077 | -3.344 | -2.271 | 1.00 | 15.84 | A |
| ATOM | 197 | H | LEU | 138 | -17.502 | -2.528 | -2.246 | 1.00 | 15.00 | A |
| ATOM | 198 | CA | LEU | 138 | -17.507 | -4.667 | -1.938 | 1.00 | 18.21 | A |
| ATOM | 199 | CB | LEU | 138 | -15.962 | -4.530 | -1.791 | 1.00 | 13.60 | A |
| ATOM | 200 | CG | LEU | 138 | -15.273 | -3.854 | -2.998 | 1.00 | 16.09 | A |
| ATOM | 201 | CD1 | LEU | 138 | -15.923 | -4.379 | -4.300 | 1.00 | 20.35 | A |
| ATOM | 202 | CD2 | LEU | 138 | -13.710 | -3.936 | -2.982 | 1.00 | 12.34 | A |
| ATOM | 203 | C | LEU | 138 | -18.170 | -5.480 | -0.772 | 1.00 | 16.29 | A |
| ATOM | 204 | O | LEU | 138 | -18.498 | -4.986 | 0.301 | 1.00 | 12.97 | A |
| ATOM | 205 | N | GLN | 139 | -18.345 | -6.768 | -1.035 | 1.00 | 13.04 | A |
| ATOM | 206 | H | GLN | 139 | -18.052 | -7.078 | -1.960 | 1.00 | 15.00 | A |
| ATOM | 207 | CA | GLN | 139 | -18.757 | -7.658 | 0.013 | 1.00 | 15.32 | A |
| ATOM | 208 | CB | GLN | 139 | -19.847 | -8.678 | -0.481 | 1.00 | 13.99 | A |
| ATOM | 209 | CG | GLN | 139 | -21.068 | -7.960 | -1.113 | 1.00 | 20.85 | A |
| ATOM | 210 | CD | GLN | 139 | -21.872 | -7.022 | -0.193 | 1.00 | 22.04 | A |
| ATOM | 211 | OE1 | GLN | 139 | -22.343 | -7.439 | 0.878 | 1.00 | 25.45 | A |
| ATOM | 212 | NE2 | GLN | 139 | -21.963 | -5.739 | -0.618 | 1.00 | 17.74 | A |
| ATOM | 213 | HE21 | GLN | 139 | -22.697 | -5.181 | -0.206 | 1.00 | 15.00 | A |
| ATOM | 214 | HE22 | GLN | 139 | -21.460 | -5.326 | -1.374 | 1.00 | 15.00 | A |
| ATOM | 215 | C | GLN | 139 | -17.527 | -8.383 | 0.541 | 1.00 | 14.26 | A |
| ATOM | 216 | O | GLN | 139 | -16.554 | -8.640 | -0.144 | 1.00 | 14.40 | A |
| ATOM | 217 | N | TRP | 140 | -17.647 | -8.780 | 1.805 | 1.00 | 12.80 | A |
| ATOM | 218 | H | TRP | 140 | -18.433 | -8.447 | 2.297 | 1.00 | 15.00 | A |
| ATOM | 219 | CA | TRP | 140 | -16.542 | -9.500 | 2.463 | 1.00 | 14.03 | A |
| ATOM | 220 | CB | TRP | 140 | -15.813 | -8.623 | 3.483 | 1.00 | 14.18 | A |
| ATOM | 221 | CG | TRP | 140 | -15.467 | -7.291 | 2.823 | 1.00 | 8.44 | A |
| ATOM | 222 | CD2 | TRP | 140 | -14.379 | -6.966 | 1.941 | 1.00 | 9.01 | A |
| ATOM | 223 | CE2 | TRP | 140 | -14.549 | -5.625 | 1.482 | 1.00 | 8.40 | A |
| ATOM | 224 | CE3 | TRP | 140 | -13.215 | -7.688 | 1.581 | 1.00 | 10.14 | A |
| ATOM | 225 | CD1 | TRP | 140 | -16.225 | -6.137 | 2.863 | 1.00 | 11.29 | A |
| ATOM | 226 | NE1 | TRP | 140 | -15.710 | -5.150 | 2.077 | 1.00 | 14.27 | A |
| ATOM | 227 | HE1 | TRP | 140 | -16.121 | -4.268 | 2.010 | 1.00 | 15.00 | A |
| ATOM | 228 | CZ2 | TRP | 140 | -13.640 | -5.009 | 0.590 | 1.00 | 8.16 | A |
| ATOM | 229 | CZ3 | TRP | 140 | -12.292 | -7.069 | 0.713 | 1.00 | 13.90 | A |
| ATOM | 230 | CH2 | TRP | 140 | -12.497 | -5.749 | 0.215 | 1.00 | 12.11 | A |
| ATOM | 231 | C | TRP | 140 | -17.016 | -10.701 | 3.170 | 1.00 | 14.34 | A |
| ATOM | 232 | O | TRP | 140 | -18.193 | -10.862 | 3.392 | 1.00 | 16.00 | A |
| ATOM | 233 | N | ALA | 141 | -16.082 | -11.528 | 3.558 | 1.00 | 14.80 | A |
| ATOM | 234 | H | ALA | 141 | -15.133 | -11.377 | 3.294 | 1.00 | 15.00 | A |
| ATOM | 235 | CA | ALA | 141 | -16.489 | -12.617 | 4.394 | 1.00 | 15.27 | A |
| ATOM | 236 | CB | ALA | 141 | -16.504 | -13.920 | 3.583 | 1.00 | 16.97 | A |
| ATOM | 237 | C | ALA | 141 | -15.585 | -12.761 | 5.607 | 1.00 | 15.90 | A |
| ATOM | 238 | O | ALA | 141 | -14.453 | -12.338 | 5.550 | 1.00 | 14.25 | A |
| ATOM | 239 | N | GLU | 142 | -16.068 | -13.366 | 6.688 | 1.00 | 19.74 | A |

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| ATOM | 240 | H | GLU | 142 | -17.055 | -13.574 | 6.688 | 1.00 | 15.00 | A |
|------|-----|------|-----|-----|---------|---------|--------|------|-------|---|
| ATOM | 241 | CA | GLU | 142 | -15.149 | -13.759 | 7.731 | 1.00 | 25.93 | A |
| ATOM | 242 | CB | GLU | 142 | -15.794 | -13.910 | 9.117 | 1.00 | 21.75 | A |
| ATOM | 243 | CG | GLU | 142 | -15.716 | -12.456 | 9.647 | 1.00 | 24.05 | A |
| ATOM | 244 | CD | GLU | 142 | -16.749 | -12.087 | 10.711 | 1.00 | 26.61 | A |
| ATOM | 245 | OE1 | GLU | 142 | -17.908 | -11.888 | 10.361 | 1.00 | 34.72 | A |
| ATOM | 246 | OE2 | GLU | 142 | -16.404 | -11.984 | 11.886 | 1.00 | 30.07 | A |
| ATOM | 247 | C | GLU | 142 | -14.200 | -14.797 | 7.193 | 1.00 | 33.25 | A |
| ATOM | 248 | O | GLU | 142 | -13.156 | -14.349 | 6.737 | 1.00 | 41.84 | A |
| ATOM | 249 | N | LYS | 143 | -14.577 | -16.080 | 7.084 | 1.00 | 34.17 | A |
| ATOM | 250 | H | LYS | 143 | -15.432 | -16.384 | 7.492 | 1.00 | 15.00 | A |
| ATOM | 251 | CA | LYS | 143 | -13.882 | -16.854 | 5.980 | 1.00 | 35.31 | A |
| ATOM | 252 | CB | LYS | 143 | -14.673 | -16.603 | 4.681 | 1.00 | 37.64 | A |
| ATOM | 253 | CG | LYS | 143 | -14.300 | -17.505 | 3.531 | 1.00 | 47.37 | A |
| ATOM | 254 | CD | LYS | 143 | -15.022 | -17.284 | 2.202 | 1.00 | 50.37 | A |
| ATOM | 255 | CE | LYS | 143 | -14.686 | -16.047 | 1.357 | 1.00 | 49.23 | A |
| ATOM | 256 | NZ | LYS | 143 | -15.632 | -16.097 | 0.221 | 1.00 | 51.67 | A |
| ATOM | 257 | HZ1 | LYS | 143 | -15.333 | -15.445 | -0.534 | 1.00 | 15.00 | A |
| ATOM | 258 | HZ2 | LYS | 143 | -15.680 | -17.061 | -0.177 | 1.00 | 15.00 | A |
| ATOM | 259 | HZ3 | LYS | 143 | -16.564 | -15.833 | 0.585 | 1.00 | 15.00 | A |
| ATOM | 260 | C | LYS | 143 | -12.330 | -16.979 | 5.637 | 1.00 | 32.80 | A |
| ATOM | 261 | O | LYS | 143 | -11.831 | -18.041 | 5.276 | 1.00 | 35.64 | A |
| ATOM | 262 | N | GLY | 144 | -11.522 | -15.923 | 5.637 | 1.00 | 28.26 | A |
| ATOM | 263 | H | GLY | 144 | -11.718 | -14.995 | 5.910 | 1.00 | 15.00 | A |
| ATOM | 264 | CA | GLY | 144 | -10.243 | -16.458 | 5.194 | 1.00 | 32.94 | A |
| ATOM | 265 | C | GLY | 144 | -9.178 | -16.862 | 6.180 | 1.00 | 29.93 | A |
| ATOM | 266 | O | GLY | 144 | -9.345 | -17.454 | 7.205 | 1.00 | 24.67 | A |
| ATOM | 267 | N | TYR | 145 | -8.069 | -16.270 | 5.815 | 1.00 | 26.37 | ·A |
| ATOM | 268 | H | TYR | 145 | -8.160 | -15.729 | 4.966 | 1.00 | 15.00 | A |
| ATOM | 269 | CA | TYR | 145 | -7.027 | -16.002 | 6.777 | 1.00 | 27.61 | A |
| ATOM | 270 | CB | TYR | 145 | -5.708 | -15.877 | 5.947 | 1.00 | 37.54 | A |
| ATOM | 271 | CG | TYR | 145 | -5.962 | -15.774 | 4.456 | 1.00 | 50.95 | A |
| ATOM | 272 | CD1 | TYR | 145 | -5.682 | -14.633 | 3.706 | 1.00 | 53.22 | A |
| ATOM | 273 | CE1 | TYR | 145 | -6.313 | -14.377 | 2.468 | 1.00 | 60.28 | A |
| ATOM | 274 | CD2 | TYR | 145 | -6.591 | -16.847 | 3.791 | 1.00 | 53.11 | A |
| ATOM | 275 | CE2 | TYR | 145 | -7.207 | -16.699 | 2.551 | 1.00 | 56.30 | A |
| ATOM | 276 | CZ | TYR | 145 | -7.162 | -15.430 | 1.873 | 1.00 | 61.12 | A |
| ATOM | 277 | OH | TYR | 145 | -7.812 | -15.119 | 0.665 | 1.00 | 62.63 | A |
| ATOM | 278 | HH | TYR | 145 | -8.575 | -15.686 | 0.401 | 1.00 | 15.00 | A |
| ATOM | 279 | C | TYR | 145 | -7.532 | -14.762 | 7.620 | 1.00 | 22.41 | A |
| ATOM | 280 | O | TYR | 145 | -7.000 | -13.677 | 7.650 | 1.00 | 22.68 | A |
| ATOM | 281 | N | TYR | 146 | -8.731 | -14.884 | 8.196 | 1.00 | 20.39 | A |
| ATOM | 282 | H | TYR | 146 | -8.935 | -15.824 | 8.509 | 1.00 | 15.00 | A |
| ATOM | 283 | CA | TYR | 146 | -9.423 | -13.700 | 8.725 | 1.00 | 20.40 | A |
| ATOM | 284 | CB | TYR | 146 | -10.886 | -13.673 | 8.306 | 1.00 | 22.53 | A |
| ATOM | 285 | CG | TYR | 146 | -11.710 | -14.460 | 9.286 | 1.00 | 23.02 | A |
| ATOM | 286 | CD1 | TYR | 146 | -11.635 | -15.873 | 9.236 | 1.00 | 26.99 | A |
| ATOM | 287 | CE1 | TYR | 146 | -12.254 | -16.623 | 10.239 | 1.00 | 25.44 | A |
| ATOM | 288 | CD2 | TYR | 146 | -12.477 | -13.766 | 10.236 | 1.00 | 23.45 | A |
| ATOM | 289 | CE2 | TYR | 146 | -13.150 | -14.520 | 11.205 | 1.00 | 26.81 | A |
| ATOM | 290 | CZ | TYR | 146 | -13.007 | -15.937 | 11.204 | 1.00 | 27.40 | A |
| ATOM | 291 | OH | TYR | 146 | -13.647 | -16.689 | 12.170 | 1.00 | 31.91 | A |
| ATOM | 292 | HH | TYR | 146 | -12.911 | -17.080 | 12.676 | 1.00 | 15.00 | A |
| ATOM | 293 | C | TYR | 146 | -9.291 | -13.419 | 10.219 | 1.00 | 18.79 | A |
| ATOM | 294 | O | TYR | 146 | -8.904 | -14.232 | 11.012 | 1.00 | 16.13 | A |
| ATOM | 295 | N | THR | 147 | -9.596 | -12.169 | 10.556 | 1.00 | 17.54 | A |
| ATOM | 296 | H | THR | 147 | -9.973 | -11.607 | 9.830 | 1.00 | 15.00 | A |
| ATOM | 297 | CA | THR | 147 | -9.432 | -11.764 | 11.948 | 1.00 | 14.06 | A |
| ATOM | 298 | CB | THR | 147 | -8.162 | -10.875 | 12.182 | 1.00 | 13.66 | A |
| ATOM | 299 | OG1 | THR | 147 | -6.912 | -11.505 | 11.856 | 1.00 | 12.56 | A |

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| ATOM | 300 | HG1 | THR | 147 | -6.934 | -11.898 | 10.980 | 1.00 | 15.00 | A |
|------|-----|-----|-----|-----|--------|---------|--------|------|-------|---|
| ATOM | 301 | CG2 | THR | 147 | -8.025 | -10.236 | 13.554 | 1.00 | 7.22 | A |
| ATOM | 302 | C | THR | 147 | -10.619 | -10.925 | 12.253 | 1.00 | 15.60 | A |
| ATOM | 303 | O | THR | 147 | -11.044 | -10.074 | 11.496 | 1.00 | 16.39 | A |
| ATOM | 304 | N | MET | 148 | -11.144 | -11.139 | 13.412 | 1.00 | 20.67 | A |
| ATOM | 305 | H | MET | 148 | -10.838 | -11.988 | 13.828 | 1.00 | 15.00 | A |
| ATOM | 306 | CA | MET | 148 | -12.124 | -10.311 | 14.110 | 1.00 | 19.71 | A |
| ATOM | 307 | CB | MET | 148 | -13.546 | -10.702 | 13.705 | 1.00 | 17.89 | A |
| ATOM | 308 | CG | MET | 148 | -14.541 | -9.580 | 14.019 | 1.00 | 13.53 | A |
| ATOM | 309 | SD | MET | 148 | -14.492 | -8.149 | 12.952 | 1.00 | 14.69 | A |
| ATOM | 310 | CE | MET | 148 | -14.566 | -8.928 | 11.333 | 1.00 | 10.10 | A |
| ATOM | 311 | C | MET | 148 | -11.915 | -10.282 | 15.639 | 1.00 | 21.49 | A |
| ATOM | 312 | O | MET | 148 | -12.594 | -10.905 | 16.436 | 1.00 | 22.98 | A |
| ATOM | 313 | N | SER | 149 | -10.955 | -9.412 | 16.055 | 1.00 | 20.58 | A |
| ATOM | 314 | H | SER | 149 | -10.516 | -8.786 | 15.406 | 1.00 | 15.00 | A |
| ATOM | 315 | CA | SER | 149 | -10.388 | -9.698 | 17.419 | 1.00 | 19.11 | A |
| ATOM | 316 | CB | SER | 149 | -9.174 | -8.860 | 17.792 | 1.00 | 12.17 | A |
| ATOM | 317 | OG | SER | 149 | -9.540 | -7.513 | 17.975 | 1.00 | 14.10 | A |
| ATOM | 318 | HG | SER | 149 | -9.571 | -7.487 | 18.934 | 1.00 | 15.00 | A |
| ATOM | 319 | C | SER | 149 | -11.203 | -9.844 | 18.727 | 1.00 | 22.19 | A |
| ATOM | 320 | O | SER | 149 | -10.728 | -10.267 | 19.772 | 1.00 | 22.95 | A |
| ATOM | 321 | N | ASN | 150 | -12.456 | -9.322 | 18.631 | 1.00 | 22.71 | A |
| ATOM | 322 | H | ASN | 150 | -12.782 | -9.247 | 17.688 | 1.00 | 15.00 | A |
| ATOM | 323 | CA | ASN | 150 | -13.361 | -9.236 | 19.764 | 1.00 | 20.32 | A |
| ATOM | 324 | CB | ASN | 150 | -12.734 | -8.446 | 20.955 | 1.00 | 21.56 | A |
| ATOM | 325 | CG | ASN | 150 | -12.343 | -6.962 | 20.706 | 1.00 | 20.71 | A |
| ATOM | 326 | OD1 | ASN | 150 | -13.059 | -6.187 | 20.119 | 1.00 | 17.81 | A |
| ATOM | 327 | ND2 | ASN | 150 | -11.222 | -6.485 | 21.271 | 1.00 | 23.86 | ·A |
| ATOM | 328 | HD21 | ASN | 150 | -11.035 | -5.521 | 21.092 | 1.00 | 15.00 | A |
| ATOM | 329 | HD22 | ASN | 150 | -10.670 | -7.109 | 21.821 | 1.00 | 15.00 | A |
| ATOM | 330 | C | ASN | 150 | -14.644 | -8.657 | 19.256 | 1.00 | 20.60 | A |
| ATOM | 331 | O | ASN | 150 | -14.718 | -8.130 | 18.148 | 1.00 | 20.56 | A |
| ATOM | 332 | N | ASN | 151 | -15.637 | -8.713 | 20.149 | 1.00 | 23.49 | A |
| ATOM | 333 | H | ASN | 151 | -15.455 | -9.124 | 21.038 | 1.00 | 15.00 | A |
| ATOM | 334 | CA | ASN | 151 | -16.974 | -8.080 | 19.823 | 1.00 | 24.71 | A |
| ATOM | 335 | CB | ASN | 151 | -18.130 | -8.645 | 20.712 | 1.00 | 28.30 | A |
| ATOM | 336 | CG | ASN | 151 | -17.959 | -8.271 | 22.173 | 1.00 | 33.23 | A |
| ATOM | 337 | OD1 | ASN | 151 | -17.075 | -7.562 | 22.606 | 1.00 | 39.79 | A |
| ATOM | 338 | ND2 | ASN | 151 | -18.782 | -8.838 | 23.011 | 1.00 | 38.32 | A |
| ATOM | 339 | HD21 | ASN | 151 | -18.553 | -8.524 | 23.928 | 1.00 | 15.00 | A |
| ATOM | 340 | HD22 | ASN | 151 | -19.495 | -9.465 | 22.733 | 1.00 | 15.00 | A |
| ATOM | 341 | C | ASN | 151 | -17.172 | -6.531 | 19.645 | 1.00 | 22.53 | A |
| ATOM | 342 | O | ASN | 151 | -18.254 | -6.048 | 19.374 | 1.00 | 21.32 | A |
| ATOM | 343 | N | LEU | 152 | -16.066 | -5.762 | 19.859 | 1.00 | 23.00 | A |
| ATOM | 344 | H | LEU | 152 | -15.247 | -6.289 | 20.070 | 1.00 | 15.00 | A |
| ATOM | 345 | CA | LEU | 152 | -15.924 | -4.335 | 19.525 | 1.00 | 18.87 | A |
| ATOM | 346 | CB | LEU | 152 | -14.830 | -3.700 | 20.325 | 1.00 | 21.77 | A |
| ATOM | 347 | CG | LEU | 152 | -14.981 | -3.999 | 21.806 | 1.00 | 24.80 | A |
| ATOM | 348 | CD1 | LEU | 152 | -16.390 | -3.645 | 22.316 | 1.00 | 22.82 | A |
| ATOM | 349 | CD2 | LEU | 152 | -13.847 | -3.256 | 22.556 | 1.00 | 23.56 | A |
| ATOM | 350 | C | LEU | 152 | -15.565 | -3.993 | 18.094 | 1.00 | 17.34 | A |
| ATOM | 351 | O | LEU | 152 | -15.590 | -2.840 | 17.708 | 1.00 | 13.39 | A |
| ATOM | 352 | N | VAL | 153 | -15.267 | -5.054 | 17.309 | 1.00 | 18.65 | A |
| ATOM | 353 | H | VAL | 153 | -15.156 | -5.962 | 17.716 | 1.00 | 15.00 | A |
| ATOM | 354 | CA | VAL | 153 | -15.439 | -4.910 | 15.849 | 1.00 | 16.81 | A |
| ATOM | 355 | CB | VAL | 153 | -14.138 | -5.021 | 14.980 | 1.00 | 15.33 | A |
| ATOM | 356 | CG1 | VAL | 153 | -12.908 | -5.718 | 15.562 | 1.00 | 21.22 | A |
| ATOM | 357 | CG2 | VAL | 153 | -13.775 | -3.757 | 14.287 | 1.00 | 16.95 | A |
| ATOM | 358 | C | VAL | 153 | -16.405 | -5.964 | 15.301 | 1.00 | 13.48 | A |
| ATOM | 359 | O | VAL | 153 | -16.363 | -7.116 | 15.647 | 1.00 | 13.06 | A |

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| ATOM | 360 | N | THR | 154 | -17.207 | -5.546 | 14.358 | 1.00 | 12.06 | A |
|------|-----|-----|-----|-----|---------|--------|--------|------|-------|---|
| ATOM | 361 | H | THR | 154 | -17.313 | -4.568 | 14.215 | 1.00 | 15.00 | A |
| ATOM | 362 | CA | THR | 154 | -17.903 | -6.600 | 13.615 | 1.00 | 16.26 | A |
| ATOM | 363 | CB | THR | 154 | -19.366 | -6.747 | 14.157 | 1.00 | 19.51 | A |
| ATOM | 364 | OG1 | THR | 154 | -19.995 | -5.459 | 14.205 | 1.00 | 19.31 | A |
| ATOM | 365 | HG1 | THR | 154 | -20.577 | -5.508 | 14.949 | 1.00 | 15.00 | A |
| ATOM | 366 | CG2 | THR | 154 | -19.502 | -7.288 | 15.571 | 1.00 | 21.62 | A |
| ATOM | 367 | C | THR | 154 | -17.997 | -6.252 | 12.107 | 1.00 | 18.12 | A |
| ATOM | 368 | O | THR | 154 | -17.992 | -5.110 | 11.605 | 1.00 | 16.55 | A |
| ATOM | 369 | N | LEU | 155 | -18.101 | -7.324 | 11.357 | 1.00 | 16.77 | A |
| ATOM | 370 | H | LEU | 155 | -18.056 | -8.202 | 11.791 | 1.00 | 15.00 | A |
| ATOM | 371 | CA | LEU | 155 | -18.514 | -7.198 | 9.967 | 1.00 | 17.10 | A |
| ATOM | 372 | CB | LEU | 155 | -17.829 | -8.353 | 9.204 | 1.00 | 20.04 | A |
| ATOM | 373 | CG | LEU | 155 | -17.524 | -8.428 | 7.692 | 1.00 | 20.81 | A |
| ATOM | 374 | CD1 | LEU | 155 | -17.822 | -7.159 | 6.908 | 1.00 | 17.03 | A |
| ATOM | 375 | CD2 | LEU | 155 | -17.912 | -9.810 | 7.139 | 1.00 | 12.42 | A |
| ATOM | 376 | C | LEU | 155 | -20.055 | -7.187 | 9.904 | 1.00 | 20.71 | A |
| ATOM | 377 | O | LEU | 155 | -20.712 | -8.163 | 10.217 | 1.00 | 18.01 | A |
| ATOM | 378 | N | GLU | 156 | -20.593 | -5.995 | 9.561 | 1.00 | 19.51 | A |
| ATOM | 379 | H | GLU | 156 | -19.959 | -5.230 | 9.440 | 1.00 | 15.00 | A |
| ATOM | 380 | CA | GLU | 156 | -22.036 | -5.888 | 9.413 | 1.00 | 21.95 | A |
| ATOM | 381 | CB | GLU | 156 | -22.641 | -4.631 | 10.033 | 1.00 | 18.95 | A |
| ATOM | 382 | CG | GLU | 156 | -22.098 | -4.412 | 11.436 | 1.00 | 27.68 | A |
| ATOM | 383 | CD | GLU | 156 | -22.721 | -5.194 | 12.587 | 1.00 | 31.62 | A |
| ATOM | 384 | OE1 | GLU | 156 | -23.347 | -6.248 | 12.367 | 1.00 | 33.40 | A |
| ATOM | 385 | OE2 | GLU | 156 | -22.532 | -4.721 | 13.724 | 1.00 | 35.00 | A |
| ATOM | 386 | C | GLU | 156 | -22.457 | -5.966 | 7.964 | 1.00 | 25.36 | A |
| ATOM | 387 | O | GLU | 156 | -21.958 | -5.298 | 7.077 | 1.00 | 22.70 | ·A |
| ATOM | 388 | N | ASN | 157 | -23.437 | -6.808 | 7.696 | 1.00 | 30.92 | A |
| ATOM | 389 | H | ASN | 157 | -23.594 | -7.590 | 8.300 | 1.00 | 15.00 | A |
| ATOM | 390 | CA | ASN | 157 | -23.804 | -6.620 | 6.300 | 1.00 | 33.31 | A |
| ATOM | 391 | CB | ASN | 157 | -23.856 | -7.970 | 5.614 | 1.00 | 31.69 | A |
| ATOM | 392 | CG | ASN | 157 | -23.669 | -7.693 | 4.168 | 1.00 | 27.70 | A |
| ATOM | 393 | OD1 | ASN | 157 | -23.397 | -6.593 | 3.810 | 1.00 | 25.89 | A |
| ATOM | 394 | ND2 | ASN | 157 | -23.893 | -8.640 | 3.275 | 1.00 | 41.69 | A |
| ATOM | 395 | HD21 | ASN | 157 | -24.069 | -9.603 | 3.467 | 1.00 | 15.00 | A |
| ATOM | 396 | HD22 | ASN | 157 | -23.745 | -8.295 | 2.340 | 1.00 | 15.00 | A |
| ATOM | 397 | C | ASN | 157 | -24.988 | -5.658 | 6.118 | 1.00 | 35.08 | A |
| ATOM | 398 | O | ASN | 157 | -26.107 | -5.949 | 6.499 | 1.00 | 37.06 | A |
| ATOM | 399 | N | GLY | 158 | -24.746 | -4.443 | 5.560 | 1.00 | 40.03 | A |
| ATOM | 400 | H | GLY | 158 | -25.601 | -3.952 | 5.429 | 1.00 | 15.00 | A |
| ATOM | 401 | CA | GLY | 158 | -23.422 | -3.887 | 5.121 | 1.00 | 38.11 | A |
| ATOM | 402 | C | GLY | 158 | -23.062 | -3.720 | 3.617 | 1.00 | 37.48 | A |
| ATOM | 403 | O | GLY | 158 | -23.890 | -3.108 | 2.950 | 1.00 | 41.11 | A |
| ATOM | 404 | N | LYS | 159 | -21.867 | -4.220 | 3.135 | 1.00 | 32.75 | A |
| ATOM | 405 | H | LYS | 159 | -21.904 | -4.134 | 2.130 | 1.00 | 15.00 | A |
| ATOM | 406 | CA | LYS | 159 | -20.828 | -4.928 | 3.962 | 1.00 | 27.83 | A |
| ATOM | 407 | CB | LYS | 159 | -20.317 | -6.122 | 3.217 | 1.00 | 28.17 | A |
| ATOM | 408 | CG | LYS | 159 | -19.734 | -7.168 | 4.069 | 1.00 | 20.48 | A |
| ATOM | 409 | CD | LYS | 159 | -20.533 | -8.426 | 4.192 | 1.00 | 29.61 | A |
| ATOM | 410 | CE | LYS | 159 | -20.577 | -9.191 | 2.869 | 1.00 | 40.41 | A |
| ATOM | 411 | NZ | LYS | 159 | -20.796 | -10.663 | 2.986 | 1.00 | 40.88 | A |
| ATOM | 412 | HZ1 | LYS | 159 | -20.739 | -11.087 | 2.035 | 1.00 | 15.00 | A |
| ATOM | 413 | HZ2 | LYS | 159 | -20.070 | -11.087 | 3.600 | 1.00 | 15.00 | A |
| ATOM | 414 | HZ3 | LYS | 159 | -21.738 | -10.848 | 3.389 | 1.00 | 15.00 | A |
| ATOM | 415 | C | LYS | 159 | -19.688 | -4.065 | 4.463 | 1.00 | 26.08 | A |
| ATOM | 416 | O | LYS | 159 | -19.023 | -3.369 | 3.696 | 1.00 | 28.01 | A |
| ATOM | 417 | N | GLN | 160 | -19.683 | -3.990 | 5.807 | 1.00 | 18.90 | A |
| ATOM | 418 | H | GLN | 160 | -20.211 | -4.674 | 6.319 | 1.00 | 15.00 | A |
| ATOM | 419 | CA | GLN | 160 | -18.922 | -2.929 | 6.464 | 1.00 | 13.89 | A |

SUBSTITUTE SHEET (RULE 26)

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| ATOM | 420 | CB | GLN | 160 | -19.778 | -1.694 | 6.611 | 1.00 | 16.79 | A |
|------|-----|------|-----|-----|---------|--------|--------|------|-------|---|
| ATOM | 421 | CG | GLN | 160 | -20.881 | -1.896 | 7.633 | 1.00 | 18.34 | A |
| ATOM | 422 | CD | GLN | 160 | -22.133 | -1.166 | 7.193 | 1.00 | 23.97 | A |
| ATOM | 423 | OE1 | GLN | 160 | -23.088 | -0.970 | 7.893 | 1.00 | 31.18 | A |
| ATOM | 424 | NE2 | GLN | 160 | -22.257 | -0.771 | 5.948 | 1.00 | 28.16 | A |
| ATOM | 425 | HE21 | GLN | 160 | -23.194 | -0.420 | 5.928 | 1.00 | 15.00 | A |
| ATOM | 426 | HE22 | GLN | 160 | -21.624 | -0.780 | 5.186 | 1.00 | 15.00 | A |
| ATOM | 427 | C | GLN | 160 | -18.313 | -3.309 | 7.777 | 1.00 | 12.87 | A |
| ATOM | 428 | O | GLN | 160 | -18.838 | -4.151 | 8.498 | 1.00 | 14.78 | A |
| ATOM | 429 | N | LEU | 161 | -17.187 | -2.637 | 8.085 | 1.00 | 11.22 | A |
| ATOM | 430 | H | LEU | 161 | -16.767 | -2.124 | 7.340 | 1.00 | 15.00 | A |
| ATOM | 431 | CA | LEU | 161 | -16.583 | -2.870 | 9.405 | 1.00 | 9.71 | A |
| ATOM | 432 | CB | LEU | 161 | -15.052 | -2.939 | 9.390 | 1.00 | 4.67 | A |
| ATOM | 433 | CG | LEU | 161 | -14.438 | -4.060 | 8.559 | 1.00 | 7.30 | A |
| ATOM | 434 | CD1 | LEU | 161 | -14.511 | -5.447 | 9.207 | 1.00 | 10.80 | A |
| ATOM | 435 | CD2 | LEU | 161 | -12.964 | -3.794 | 8.389 | 1.00 | 5.48 | A |
| ATOM | 436 | C | LEU | 161 | -17.082 | -1.836 | 10.412 | 1.00 | 10.17 | A |
| ATOM | 437 | O | LEU | 161 | -16.826 | -0.657 | 10.341 | 1.00 | 13.36 | A |
| ATOM | 438 | N | THR | 162 | -17.848 | -2.338 | 11.375 | 1.00 | 16.94 | A |
| ATOM | 439 | H | THR | 162 | -18.153 | -3.279 | 11.251 | 1.00 | 15.00 | ·A |
| ATOM | 440 | CA | THR | 162 | -18.317 | -1.480 | 12.493 | 1.00 | 16.14 | A |
| ATOM | 441 | CB | THR | 162 | -19.807 | -1.769 | 12.640 | 1.00 | 13.33 | A |
| ATOM | 442 | OG1 | THR | 162 | -20.339 | -1.707 | 11.308 | 1.00 | 16.73 | A |
| ATOM | 443 | HG1 | THR | 162 | -21.211 | -1.254 | 11.343 | 1.00 | 15.00 | A |
| ATOM | 444 | CG2 | THR | 162 | -20.553 | -0.832 | 13.562 | 1.00 | 15.01 | A |
| ATOM | 445 | C | THR | 162 | -17.531 | -1.547 | 13.842 | 1.00 | 13.28 | A |
| ATOM | 446 | O | THR | 162 | -17.358 | -2.587 | 14.449 | 1.00 | 20.21 | A |
| ATOM | 447 | N | VAL | 163 | -16.994 | -0.437 | 14.282 | 1.00 | 14.22 | ·A |
| ATOM | 448 | H | VAL | 163 | -16.859 | 0.243 | 13.567 | 1.00 | 15.00 | A |
| ATOM | 449 | CA | VAL | 163 | -16.326 | -0.358 | 15.586 | 1.00 | 15.72 | A |
| ATOM | 450 | CB | VAL | 163 | -15.038 | 0.426 | 15.428 | 1.00 | 11.82 | A |
| ATOM | 451 | CG1 | VAL | 163 | -15.191 | 1.944 | 15.368 | 1.00 | 9.87 | A |
| ATOM | 452 | CG2 | VAL | 163 | -14.229 | -0.124 | 14.245 | 1.00 | 18.88 | A |
| ATOM | 453 | C | VAL | 163 | -17.193 | 0.283 | 16.706 | 1.00 | 17.93 | A |
| ATOM | 454 | O | VAL | 163 | -18.001 | 1.180 | 16.453 | 1.00 | 20.25 | A |
| ATOM | 455 | N | LYS | 164 | -17.037 | -0.232 | 17.925 | 1.00 | 15.44 | A |
| ATOM | 456 | H | LYS | 164 | -16.254 | -0.858 | 18.020 | 1.00 | 15.00 | A |
| ATOM | 457 | CA | LYS | 164 | -17.856 | 0.138 | 19.109 | 1.00 | 17.33 | A |
| ATOM | 458 | CB | LYS | 164 | -18.351 | -1.150 | 19.807 | 1.00 | 19.58 | A |
| ATOM | 459 | CG | LYS | 164 | -19.214 | -1.885 | 18.759 | 1.00 | 23.56 | A |
| ATOM | 460 | CD | LYS | 164 | -19.417 | -3.410 | 18.851 | 1.00 | 28.85 | A |
| ATOM | 461 | CE | LYS | 164 | -20.039 | -4.047 | 17.554 | 1.00 | 33.81 | A |
| ATOM | 462 | NZ | LYS | 164 | -19.428 | -3.681 | 16.227 | 1.00 | 18.98 | A |
| ATOM | 463 | HZ1 | LYS | 164 | -19.195 | -2.667 | 16.222 | 1.00 | 15.00 | A |
| ATOM | 464 | HZ2 | LYS | 164 | -18.552 | -4.223 | 16.092 | 1.00 | 15.00 | A |
| ATOM | 465 | HZ3 | LYS | 164 | -20.084 | -3.888 | 15.445 | 1.00 | 15.00 | A |
| ATOM | 466 | C | LYS | 164 | -17.193 | 1.099 | 20.056 | 1.00 | 15.14 | A |
| ATOM | 467 | O | LYS | 164 | -17.712 | 1.588 | 21.048 | 1.00 | 17.72 | A |
| ATOM | 468 | N | ARG | 165 | -15.992 | 1.428 | 19.621 | 1.00 | 17.49 | A |
| ATOM | 469 | H | ARG | 165 | -15.550 | 0.838 | 18.932 | 1.00 | 15.00 | A |
| ATOM | 470 | CA | ARG | 165 | -15.184 | 2.415 | 20.325 | 1.00 | 20.18 | A |
| ATOM | 471 | CB | ARG | 165 | -13.985 | 1.806 | 21.049 | 1.00 | 24.65 | A |
| ATOM | 472 | CG | ARG | 165 | -14.363 | 0.833 | 22.126 | 1.00 | 29.54 | A |
| ATOM | 473 | CD | ARG | 165 | -13.274 | 1.077 | 23.145 | 1.00 | 38.82 | A |
| ATOM | 474 | NE | ARG | 165 | -13.719 | 1.998 | 24.186 | 1.00 | 43.41 | A |
| ATOM | 475 | HE | ARG | 165 | -14.331 | 1.671 | 24.908 | 1.00 | 15.00 | A |
| ATOM | 476 | CZ | ARG | 165 | -13.190 | 3.250 | 24.362 | 1.00 | 44.06 | A |
| ATOM | 477 | NH1 | ARG | 165 | -13.406 | 3.765 | 25.562 | 1.00 | 41.25 | A |
| ATOM | 478 | HH11 | ARG | 165 | -13.054 | 4.683 | 25.763 | 1.00 | 15.00 | A |
| ATOM | 479 | HH12 | ARG | 165 | -13.919 | 3.249 | 26.250 | 1.00 | 15.00 | A |

| ATOM | 480 | NH2 | ARG | 165 | -12.485 | 3.946 | 23.425 | 1.00 | 31.65 | A |
|------|-----|------|-----|-----|---------|-------|--------|------|-------|---|
| ATOM | 481 | HH21 | ARG | 165 | -12.133 | 4.860 | 23.623 | 1.00 | 15.00 | A |
| ATOM | 482 | HH22 | ARG | 165 | -12.322 | 3.527 | 22.530 | 1.00 | 15.00 | A |
| ATOM | 483 | C | ARG | 165 | -14.608 | 3.554 | 19.510 | 1.00 | 17.70 | A |
| ATOM | 484 | O | ARG | 165 | -14.018 | 3.450 | 18.441 | 1.00 | 18.26 | A |
| ATOM | 485 | N | GLN | 166 | -14.763 | 4.687 | 20.151 | 1.00 | 17.43 | A |
| ATOM | 486 | H | GLN | 166 | -15.263 | 4.614 | 21.007 | 1.00 | 15.00 | A |
| ATOM | 487 | CA | GLN | 166 | -14.138 | 5.911 | 19.698 | 1.00 | 19.00 | A |
| ATOM | 488 | CB | GLN | 166 | -14.613 | 7.021 | 20.610 | 1.00 | 23.79 | A |
| ATOM | 489 | CG | GLN | 166 | -14.067 | 8.409 | 20.386 | 1.00 | 34.06 | A |
| ATOM | 490 | CD | GLN | 166 | -15.178 | 9.399 | 20.659 | 1.00 | 45.91 | A |
| ATOM | 491 | OE1 | GLN | 166 | -15.102 | 10.492 | 20.135 | 1.00 | 53.64 | A |
| ATOM | 492 | NE2 | GLN | 166 | -16.202 | 9.046 | 21.418 | 1.00 | 44.10 | A |
| ATOM | 493 | HE21 | GLN | 166 | -16.906 | 9.765 | 21.443 | 1.00 | 15.00 | A |
| ATOM | 494 | HE22 | GLN | 166 | -16.577 | 8.287 | 21.935 | 1.00 | 15.00 | A |
| ATOM | 495 | C | GLN | 166 | -12.649 | 5.881 | 19.644 | 1.00 | 17.48 | A |
| ATOM | 496 | O | GLN | 166 | -12.029 | 5.378 | 20.561 | 1.00 | 18.13 | A |
| ATOM | 497 | N | GLY | 167 | -12.160 | 6.478 | 18.565 | 1.00 | 14.83 | A |
| ATOM | 498 | H | GLY | 167 | -12.750 | 6.836 | 17.850 | 1.00 | 15.00 | A |
| ATOM | 499 | CA | GLY | 167 | -10.728 | 6.711 | 18.557 | 1.00 | 16.28 | A |
| ATOM | 500 | C | GLY | 167 | -10.044 | 6.685 | 17.204 | 1.00 | 16.48 | A |
| ATOM | 501 | O | GLY | 167 | -10.674 | 6.601 | 16.162 | 1.00 | 19.19 | A |
| ATOM | 502 | N | LEU | 168 | -8.720 | 6.735 | 17.209 | 1.00 | 17.06 | A |
| ATOM | 503 | H | LEU | 168 | -8.311 | 6.890 | 18.120 | 1.00 | 15.00 | A |
| ATOM | 504 | CA | LEU | 168 | -7.925 | 6.625 | 15.992 | 1.00 | 16.60 | A |
| ATOM | 505 | CB | LEU | 168 | -6.600 | 7.343 | 16.289 | 1.00 | 21.87 | A |
| ATOM | 506 | CG | LEU | 168 | -6.247 | 8.745 | 15.716 | 1.00 | 22.69 | A |
| ATOM | 507 | CD1 | LEU | 168 | -5.119 | 9.410 | 16.539 | 1.00 | 21.20 | ·A |
| ATOM | 508 | CD2 | LEU | 168 | -7.436 | 9.617 | 15.361 | 1.00 | 18.38 | A |
| ATOM | 509 | C | LEU | 168 | -7.686 | 5.136 | 15.604 | 1.00 | 14.84 | A |
| ATOM | 510 | O | LEU | 168 | -7.282 | 4.278 | 16.392 | 1.00 | 15.89 | A |
| ATOM | 511 | N | TYR | 169 | -7.943 | 4.873 | 14.300 | 1.00 | 10.57 | A |
| ATOM | 512 | H | TYR | 169 | -8.313 | 5.659 | 13.807 | 1.00 | 15.00 | A |
| ATOM | 513 | CA | TYR | 169 | -7.683 | 3.572 | 13.656 | 1.00 | 5.27 | A |
| ATOM | 514 | CB | TYR | 169 | -8.989 | 3.014 | 13.230 | 1.00 | 5.83 | A |
| ATOM | 515 | CG | TYR | 169 | -9.857 | 2.620 | 14.423 | 1.00 | 6.94 | A |
| ATOM | 516 | CD1 | TYR | 169 | -10.524 | 3.598 | 15.168 | 1.00 | 7.40 | A |
| ATOM | 517 | CE1 | TYR | 169 | -11.390 | 3.193 | 16.218 | 1.00 | 7.77 | A |
| ATOM | 518 | CD2 | TYR | 169 | -10.016 | 1.255 | 14.744 | 1.00 | 8.89 | A |
| ATOM | 519 | CE2 | TYR | 169 | -10.850 | 0.841 | 15.804 | 1.00 | 9.40 | A |
| ATOM | 520 | CZ | TYR | 169 | -11.563 | 1.827 | 16.534 | 1.00 | 10.39 | A |
| ATOM | 521 | OH | TYR | 169 | -12.443 | 1.410 | 17.534 | 1.00 | 7.99 | A |
| ATOM | 522 | HH | TYR | 169 | -13.009 | 2.117 | 17.800 | 1.00 | 15.00 | A |
| ATOM | 523 | C | TYR | 169 | -6.810 | 3.642 | 12.390 | 1.00 | 6.72 | A |
| ATOM | 524 | O | TYR | 169 | -6.917 | 4.498 | 11.557 | 1.00 | 9.12 | A |
| ATOM | 525 | N | TYR | 170 | -5.899 | 2.722 | 12.228 | 1.00 | 9.53 | A |
| ATOM | 526 | H | TYR | 170 | -5.806 | 2.081 | 12.986 | 1.00 | 15.00 | A |
| ATOM | 527 | CA | TYR | 170 | -5.313 | 2.511 | 10.899 | 1.00 | 10.01 | A |
| ATOM | 528 | CB | TYR | 170 | -3.967 | 1.797 | 11.044 | 1.00 | 7.46 | A |
| ATOM | 529 | CG | TYR | 170 | -3.259 | 1.636 | 9.679 | 1.00 | 13.45 | A |
| ATOM | 530 | CD1 | TYR | 170 | -2.680 | 2.766 | 9.052 | 1.00 | 12.66 | A |
| ATOM | 531 | CE1 | TYR | 170 | -2.213 | 2.658 | 7.738 | 1.00 | 10.18 | A |
| ATOM | 532 | CD2 | TYR | 170 | -3.304 | 0.385 | 9.057 | 1.00 | 10.90 | A |
| ATOM | 533 | CE2 | TYR | 170 | -2.891 | 0.303 | 7.730 | 1.00 | 8.68 | A |
| ATOM | 534 | CZ | TYR | 170 | -2.331 | 1.419 | 7.124 | 1.00 | 9.97 | A |
| ATOM | 535 | OH | TYR | 170 | -1.774 | 1.286 | 5.859 | 1.00 | 17.50 | A |
| ATOM | 536 | HH | TYR | 170 | -1.886 | 0.404 | 5.514 | 1.00 | 15.00 | A |
| ATOM | 537 | C | TYR | 170 | -6.279 | 1.610 | 10.073 | 1.00 | 10.40 | A |
| ATOM | 538 | O | TYR | 170 | -6.679 | 0.500 | 10.421 | 1.00 | 12.52 | A |
| ATOM | 539 | N | ILE | 171 | -6.704 | 2.174 | 8.968 | 1.00 | 12.16 | A |

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| ATOM | 540 | H | ILE | 171 | -6.475 | 3.135 | 8.808 | 1.00 | 15.00 | A |
|------|-----|-----|-----|-----|--------|--------|--------|------|-------|---|
| ATOM | 541 | CA | ILE | 171 | -7.608 | 1.430 | 8.138 | 1.00 | 9.37 | A |
| ATOM | 542 | CB | ILE | 171 | -9.070 | 1.990 | 8.317 | 1.00 | 11.21 | A |
| ATOM | 543 | CG2 | ILE | 171 | -9.326 | 3.501 | 8.677 | 1.00 | 17.27 | A |
| ATOM | 544 | CG1 | ILE | 171 | -10.046 | 1.564 | 7.214 | 1.00 | 13.33 | A |
| ATOM | 545 | CD1 | ILE | 171 | -10.647 | 0.250 | 7.619 | 1.00 | 17.53 | A |
| ATOM | 546 | C | ILE | 171 | -7.074 | 1.234 | 6.694 | 1.00 | 8.34 | A |
| ATOM | 547 | O | ILE | 171 | -6.453 | 2.088 | 6.082 | 1.00 | 6.96 | A |
| ATOM | 548 | N | TYR | 172 | -7.286 | 0.005 | 6.216 | 1.00 | 11.07 | A |
| ATOM | 549 | H | TYR | 172 | -7.809 | -0.624 | 6.786 | 1.00 | 15.00 | A |
| ATOM | 550 | CA | TYR | 172 | -6.708 | -0.378 | 4.922 | 1.00 | 15.60 | A |
| ATOM | 551 | CB | TYR | 172 | -5.332 | -1.082 | 5.037 | 1.00 | 14.32 | A |
| ATOM | 552 | CG | TYR | 172 | -5.389 | -2.397 | 5.796 | 1.00 | 9.21 | A |
| ATOM | 553 | CD1 | TYR | 172 | -5.342 | -2.402 | 7.216 | 1.00 | 12.52 | A |
| ATOM | 554 | CE1 | TYR | 172 | -5.607 | -3.620 | 7.901 | 1.00 | 10.88 | A |
| ATOM | 555 | CD2 | TYR | 172 | -5.565 | -3.586 | 5.050 | 1.00 | 12.66 | A |
| ATOM | 556 | CE2 | TYR | 172 | -5.829 | -4.800 | 5.740 | 1.00 | 15.83 | A |
| ATOM | 557 | CZ | TYR | 172 | -5.822 | -4.808 | 7.164 | 1.00 | 11.94 | A |
| ATOM | 558 | OH | TYR | 172 | -5.995 | -6.002 | 7.820 | 1.00 | 12.17 | A |
| ATOM | 559 | HH | TYR | 172 | -6.433 | -5.843 | 8.657 | 1.00 | 15.00 | A |
| ATOM | 560 | C | TYR | 172 | -7.605 | -1.276 | 4.106 | 1.00 | 16.85 | A |
| ATOM | 561 | O | TYR | 172 | -8.346 | -2.057 | 4.692 | 1.00 | 14.06 | A |
| ATOM | 562 | N | ALA | 173 | -7.448 | -1.141 | 2.776 | 1.00 | 16.29 | A |
| ATOM | 563 | H | ALA | 173 | -6.751 | -0.490 | 2.503 | 1.00 | 15.00 | A |
| ATOM | 564 | CA | ALA | 173 | -7.940 | -2.152 | 1.836 | 1.00 | 15.11 | A |
| ATOM | 565 | CB | ALA | 173 | -9.300 | -1.725 | 1.292 | 1.00 | 12.08 | A |
| ATOM | 566 | C | ALA | 173 | -7.007 | -2.537 | 0.653 | 1.00 | 15.86 | A |
| ATOM | 567 | O | ALA | 173 | -6.147 | -1.806 | 0.191 | 1.00 | 14.20 | A |
| ATOM | 568 | N | GLN | 174 | -7.244 | -3.714 | 0.109 | 1.00 | 16.56 | A |
| ATOM | 569 | H | GLN | 174 | -7.774 | -4.389 | 0.620 | 1.00 | 15.00 | A |
| ATOM | 570 | CA | GLN | 174 | -6.470 | -4.119 | -1.070 | 1.00 | 19.25 | A |
| ATOM | 571 | CB | GLN | 174 | -5.582 | -5.292 | -0.832 | 1.00 | 21.99 | A |
| ATOM | 572 | CG | GLN | 174 | -4.205 | -4.727 | -1.030 | 1.00 | 30.99 | A |
| ATOM | 573 | CD | GLN | 174 | -3.174 | -5.845 | -0.979 | 1.00 | 34.25 | A |
| ATOM | 574 | OE1 | GLN | 174 | -2.308 | -5.899 | -0.105 | 1.00 | 32.91 | A |
| ATOM | 575 | NE2 | GLN | 174 | -3.268 | -6.699 | -2.014 | 1.00 | 31.50 | A |
| ATOM | 576 | HE21 | GLN | 174 | -2.668 | -7.487 | -1.970 | 1.00 | 15.00 | A |
| ATOM | 577 | HE22 | GLN | 174 | -3.973 | -6.621 | -2.714 | 1.00 | 15.00 | A |
| ATOM | 578 | C | GLN | 174 | -7.413 | -4.644 | -2.114 | 1.00 | 19.20 | A |
| ATOM | 579 | O | GLN | 174 | -8.285 | -5.434 | -1.880 | 1.00 | 20.03 | A |
| ATOM | 580 | N | VAL | 175 | -7.291 | -4.107 | -3.301 | 1.00 | 19.28 | A |
| ATOM | 581 | H | VAL | 175 | -6.594 | -3.401 | -3.400 | 1.00 | 15.00 | A |
| ATOM | 582 | CA | VAL | 175 | -8.247 | -4.500 | -4.323 | 1.00 | 22.43 | A |
| ATOM | 583 | CB | VAL | 175 | -9.319 | -3.409 | -4.644 | 1.00 | 21.41 | A |
| ATOM | 584 | CG1 | VAL | 175 | -10.146 | -2.830 | -3.495 | 1.00 | 20.17 | A |
| ATOM | 585 | CG2 | VAL | 175 | -10.268 | -4.061 | -5.639 | 1.00 | 22.88 | A |
| ATOM | 586 | C | VAL | 175 | -7.508 | -4.859 | -5.615 | 1.00 | 24.56 | A |
| ATOM | 587 | O | VAL | 175 | -6.928 | -3.997 | -6.301 | 1.00 | 23.28 | A |
| ATOM | 588 | N | THR | 176 | -7.563 | -6.180 | -5.879 | 1.00 | 25.40 | A |
| ATOM | 589 | H | THR | 176 | -7.994 | -6.850 | -5.250 | 1.00 | 15.00 | A |
| ATOM | 590 | CA | THR | 176 | -7.086 | -6.501 | -7.222 | 1.00 | 24.46 | A |
| ATOM | 591 | CB | THR | 176 | -5.844 | -7.454 | -7.256 | 1.00 | 24.78 | A |
| ATOM | 592 | OG1 | THR | 176 | -5.948 | -8.650 | -8.028 | 1.00 | 20.31 | A |
| ATOM | 593 | HG1 | THR | 176 | -5.250 | -9.253 | -7.796 | 1.00 | 15.00 | A |
| ATOM | 594 | CG2 | THR | 176 | -5.329 | -7.711 | -5.867 | 1.00 | 17.07 | A |
| ATOM | 595 | C | THR | 176 | -8.178 | -6.700 | -8.272 | 1.00 | 25.44 | A |
| ATOM | 596 | O | THR | 176 | -9.326 | -7.043 | -7.995 | 1.00 | 26.86 | A |
| ATOM | 597 | N | PHE | 177 | -7.855 | -6.341 | -9.506 | 1.00 | 22.44 | A |
| ATOM | 598 | H | PHE | 177 | -6.920 | -6.083 | -9.732 | 1.00 | 15.00 | A |
| ATOM | 599 | CA | PHE | 177 | -8.939 | -6.511 | -10.479 | 1.00 | 22.70 | A |

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| ATOM | 600 | CB | PHE | 177 | -9.746 | -5.194 | -10.599 | 1.00 | 20.90 | A |
|------|-----|-----|-----|-----|--------|--------|---------|------|-------|---|
| ATOM | 601 | CG | PHE | 177 | -8.813 | -4.034 | -10.927 | 1.00 | 22.51 | A |
| ATOM | 602 | CD1 | PHE | 177 | -8.771 | -3.548 | -12.252 | 1.00 | 22.11 | A |
| ATOM | 603 | CD2 | PHE | 177 | -8.011 | -3.422 | -9.920 | 1.00 | 21.87 | A |
| ATOM | 604 | CE1 | PHE | 177 | -8.041 | -2.387 | -12.550 | 1.00 | 20.53 | A |
| ATOM | 605 | CE2 | PHE | 177 | -7.289 | -2.247 | -10.204 | 1.00 | 20.44 | A |
| ATOM | 606 | CZ | PHE | 177 | -7.376 | -1.713 | -11.500 | 1.00 | 22.79 | A |
| ATOM | 607 | C | PHE | 177 | -8.381 | -6.949 | -11.800 | 1.00 | 22.14 | A |
| ATOM | 608 | O | PHE | 177 | -7.219 | -6.695 | -12.072 | 1.00 | 21.60 | A |
| ATOM | 609 | N | CYS | 178 | -9.210 | -7.555 | -12.625 | 1.00 | 24.52 | A |
| ATOM | 610 | H | CYS | 178 | -10.146 | -7.797 | -12.370 | 1.00 | 15.00 | A |
| ATOM | 611 | CA | CYS | 178 | -8.599 | -7.849 | -13.942 | 1.00 | 29.77 | A |
| ATOM | 612 | CB | CYS | 178 | -8.501 | -9.365 | -14.214 | 1.00 | 32.06 | A |
| ATOM | 613 | SG | CYS | 178 | -7.685 | -9.731 | -15.792 | 1.00 | 35.17 | A |
| ATOM | 614 | C | CYS | 178 | -9.323 | -7.146 | -15.088 | 1.00 | 28.41 | A |
| ATOM | 615 | O | CYS | 178 | -10.534 | -7.247 | -15.185 | 1.00 | 27.54 | A |
| ATOM | 616 | N | SER | 179 | -8.589 | -6.393 | -15.910 | 1.00 | 28.86 | A |
| ATOM | 617 | H | SER | 179 | -7.608 | -6.271 | -15.754 | 1.00 | 15.00 | A |
| ATOM | 618 | CA | SER | 179 | -9.374 | -5.454 | -16.704 | 1.00 | 29.01 | A |
| ATOM | 619 | CB | SER | 179 | -9.379 | -4.118 | -16.020 | 1.00 | 30.82 | A |
| ATOM | 620 | OG | SER | 179 | -10.615 | -3.492 | -16.319 | 1.00 | 39.79 | A |
| ATOM | 621 | HG | SER | 179 | -10.725 | -2.812 | -15.667 | 1.00 | 15.00 | A |
| ATOM | 622 | C | SER | 179 | -9.063 | -5.196 | -18.165 | 1.00 | 31.16 | A |
| ATOM | 623 | O | SER | 179 | -7.931 | -4.953 | -18.537 | 1.00 | 28.58 | A |
| ATOM | 624 | N | ASN | 180 | -10.083 | -5.255 | -19.042 | 1.00 | 35.32 | A |
| ATOM | 625 | H | ASN | 180 | -10.966 | -5.700 | -18.834 | 1.00 | 15.00 | A |
| ATOM | 626 | CA | ASN | 180 | -9.782 | -4.725 | -20.366 | 1.00 | 34.74 | A |
| ATOM | 627 | CB | ASN | 180 | -10.205 | -5.554 | -21.589 | 1.00 | 37.96 | A |
| ATOM | 628 | CG | ASN | 180 | -9.650 | -4.980 | -22.896 | 1.00 | 37.12 | A |
| ATOM | 629 | OD1 | ASN | 180 | -10.058 | -3.947 | -23.356 | 1.00 | 40.66 | A |
| ATOM | 630 | ND2 | ASN | 180 | -8.619 | -5.536 | -23.456 | 1.00 | 35.85 | A |
| ATOM | 631 | HD21 | ASN | 180 | -8.343 | -6.475 | -23.306 | 1.00 | 15.00 | A |
| ATOM | 632 | HD22 | ASN | 180 | -8.153 | -4.891 | -24.065 | 1.00 | 15.00 | A |
| ATOM | 633 | C | ASN | 180 | -10.197 | -3.331 | -20.588 | 1.00 | 36.96 | A |
| ATOM | 634 | O | ASN | 180 | -11.314 | -2.894 | -20.433 | 1.00 | 37.89 | A |
| ATOM | 635 | N | ARG | 181 | -9.147 | -2.699 | -21.068 | 1.00 | 41.95 | A |
| ATOM | 636 | H | ARG | 181 | -8.363 | -3.318 | -21.141 | 1.00 | 15.00 | A |
| ATOM | 637 | CA | ARG | 181 | -8.997 | -1.313 | -21.489 | 1.00 | 44.24 | A |
| ATOM | 638 | CB | ARG | 181 | -7.563 | -1.279 | -22.026 | 1.00 | 43.43 | A |
| ATOM | 639 | CG | ARG | 181 | -6.348 | -1.638 | -21.101 | 1.00 | 45.11 | A |
| ATOM | 640 | CD | ARG | 181 | -6.235 | -2.853 | -20.134 | 1.00 | 40.68 | A |
| ATOM | 641 | NE | ARG | 181 | -5.064 | -2.772 | -19.271 | 1.00 | 46.11 | A |
| ATOM | 642 | HE | ARG | 181 | -4.991 | -2.058 | -18.578 | 1.00 | 15.00 | A |
| ATOM | 643 | CZ | ARG | 181 | -4.024 | -3.611 | -19.432 | 1.00 | 49.77 | A |
| ATOM | 644 | NH1 | ARG | 181 | -2.886 | -3.414 | -18.790 | 1.00 | 54.33 | A |
| ATOM | 645 | HH11 | ARG | 181 | -2.113 | -4.032 | -18.918 | 1.00 | 15.00 | A |
| ATOM | 646 | HH12 | ARG | 181 | -2.807 | -2.642 | -18.161 | 1.00 | 15.00 | A |
| ATOM | 647 | NH2 | ARG | 181 | -4.085 | -4.641 | -20.247 | 1.00 | 54.26 | A |
| ATOM | 648 | HH21 | ARG | 181 | -3.286 | -5.230 | -20.354 | 1.00 | 15.00 | A |
| ATOM | 649 | HH22 | ARG | 181 | -4.918 | -4.833 | -20.761 | 1.00 | 15.00 | A |
| ATOM | 650 | C | ARG | 181 | -10.049 | -0.866 | -22.499 | 1.00 | 47.10 | A |
| ATOM | 651 | O | ARG | 181 | -10.979 | -0.112 | -22.227 | 1.00 | 49.20 | A |
| ATOM | 652 | N | GLU | 182 | -9.895 | -1.447 | -23.690 | 1.00 | 49.64 | A |
| ATOM | 653 | H | GLU | 182 | -9.201 | -2.166 | -23.775 | 1.00 | 15.00 | A |
| ATOM | 654 | CA | GLU | 182 | -10.976 | -1.385 | -24.676 | 1.00 | 52.41 | A |
| ATOM | 655 | CB | GLU | 182 | -10.437 | -2.020 | -25.970 | 1.00 | 56.93 | A |
| ATOM | 656 | CG | GLU | 182 | -10.932 | -1.418 | -27.295 | 1.00 | 66.05 | A |
| ATOM | 657 | CD | GLU | 182 | -10.758 | 0.116 | -27.327 | 1.00 | 70.54 | A |
| ATOM | 658 | OE1 | GLU | 182 | -9.613 | 0.586 | -27.442 | 1.00 | 72.98 | A |
| ATOM | 659 | OE2 | GLU | 182 | -11.778 | 0.830 | -27.244 | 1.00 | 72.46 | A |

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| ATOM | 660 | C    | GLU | 182 | -12.388 | -1.934 | -24.304 | 1.00 | 53.00 | A |
|------|-----|------|-----|-----|---------|--------|---------|------|-------|---|
| ATOM | 661 | O    | GLU | 182 | -13.379 | -1.492 | -24.862 | 1.00 | 54.27 | A |
| ATOM | 662 | N    | ALA | 183 | -12.505 | -2.877 | -23.335 | 1.00 | 52.34 | A |
| ATOM | 663 | H    | ALA | 183 | -11.676 | -3.173 | -22.865 | 1.00 | 15.00 | A |
| ATOM | 664 | CA   | ALA | 183 | -13.867 | -3.258 | -22.899 | 1.00 | 50.19 | A |
| ATOM | 665 | CB   | ALA | 183 | -13.855 | -4.721 | -22.447 | 1.00 | 45.02 | A |
| ATOM | 666 | C    | ALA | 183 | -14.562 | -2.321 | -21.867 | 1.00 | 50.66 | A |
| ATOM | 667 | O    | ALA | 183 | -15.712 | -1.945 | -21.990 | 1.00 | 47.77 | A |
| ATOM | 668 | N    | SER | 184 | -13.773 | -1.888 | -20.878 | 1.00 | 52.95 | A |
| ATOM | 669 | H    | SER | 184 | -12.826 | -2.172 | -20.991 | 1.00 | 15.00 | A |
| ATOM | 670 | CA   | SER | 184 | -14.228 | -1.043 | -19.729 | 1.00 | 56.78 | A |
| ATOM | 671 | CB   | SER | 184 | -13.384 | -1.397 | -18.481 | 1.00 | 53.58 | A |
| ATOM | 672 | OG   | SER | 184 | -13.975 | -2.448 | -17.721 | 1.00 | 47.46 | A |
| ATOM | 673 | HG   | SER | 184 | -13.291 | -3.019 | -17.388 | 1.00 | 15.00 | A |
| ATOM | 674 | C    | SER | 184 | -14.183 | 0.517  | -19.880 | 1.00 | 59.95 | A |
| ATOM | 675 | O    | SER | 184 | -13.913 | 1.297  | -18.964 | 1.00 | 65.25 | A |
| ATOM | 676 | N    | SER | 185 | -14.324 | 0.995  | -21.131 | 1.00 | 60.08 | A |
| ATOM | 677 | H    | SER | 185 | -14.623 | 0.345  | -21.831 | 1.00 | 15.00 | A |
| ATOM | 678 | CA   | SER | 185 | -13.825 | 2.375  | -21.391 | 1.00 | 60.12 | A |
| ATOM | 679 | CB   | SER | 185 | -13.522 | 2.640  | -22.869 | 1.00 | 60.49 | A |
| ATOM | 680 | OG   | SER | 185 | -12.243 | 2.098  | -23.242 | 1.00 | 59.80 | A |
| ATOM | 681 | HG   | SER | 185 | -12.158 | 1.234  | -22.833 | 1.00 | 15.00 | A |
| ATOM | 682 | C    | SER | 185 | -14.580 | 3.589  | -20.885 | 1.00 | 59.59 | A |
| ATOM | 683 | O    | SER | 185 | -15.437 | 4.159  | -21.543 | 1.00 | 60.08 | A |
| ATOM | 684 | N    | GLN | 186 | -14.200 | 3.990  | -19.670 | 1.00 | 57.71 | A |
| ATOM | 685 | H    | GLN | 186 | -13.601 | 3.376  | -19.153 | 1.00 | 15.00 | A |
| ATOM | 686 | CA   | GLN | 186 | -15.121 | 4.936  | -18.993 | 1.00 | 57.00 | A |
| ATOM | 687 | CB   | GLN | 186 | -16.094 | 4.062  | -18.175 | 1.00 | 58.66 | ·A |
| ATOM | 688 | CG   | GLN | 186 | -15.355 | 3.354  | -17.050 | 1.00 | 59.69 | A |
| ATOM | 689 | CD   | GLN | 186 | -16.369 | 2.789  | -16.088 | 1.00 | 59.92 | A |
| ATOM | 690 | OE1  | GLN | 186 | -17.270 | 3.513  | -15.687 | 1.00 | 59.81 | A |
| ATOM | 691 | NE2  | GLN | 186 | -16.249 | 1.503  | -15.787 | 1.00 | 59.63 | A |
| ATOM | 692 | HE21 | GLN | 186 | -15.492 | 0.948  | -16.113 | 1.00 | 15.00 | A |
| ATOM | 693 | HE22 | GLN | 186 | -16.950 | 1.119  | -15.168 | 1.00 | 15.00 | A |
| ATOM | 694 | C    | GLN | 186 | -14.758 | 6.290  | -18.221 | 1.00 | 54.36 | A |
| ATOM | 695 | O    | GLN | 186 | -15.596 | 7.198  | -18.298 | 1.00 | 53.98 | A |
| ATOM | 696 | N    | ALA | 187 | -13.566 | 6.424  | -17.511 | 1.00 | 50.35 | A |
| ATOM | 697 | H    | ALA | 187 | -13.476 | 7.274  | -16.970 | 1.00 | 15.00 | A |
| ATOM | 698 | CA   | ALA | 187 | -12.388 | 5.599  | -17.832 | 1.00 | 43.26 | A |
| ATOM | 699 | CB   | ALA | 187 | -11.546 | 6.284  | -18.918 | 1.00 | 38.95 | A |
| ATOM | 700 | C    | ALA | 187 | -11.456 | 4.882  | -16.849 | 1.00 | 40.48 | A |
| ATOM | 701 | O    | ALA | 187 | -10.887 | 3.875  | -17.295 | 1.00 | 43.24 | A |
| ATOM | 702 | N    | PRO | 188 | -11.210 | 5.383  | -15.594 | 1.00 | 38.66 | A |
| ATOM | 703 | CD   | PRO | 188 | -11.543 | 6.687  | -15.000 | 1.00 | 38.15 | A |
| ATOM | 704 | CA   | PRO | 188 | -10.220 | 4.665  | -14.751 | 1.00 | 35.94 | A |
| ATOM | 705 | CB   | PRO | 188 | -9.395  | 5.813  | -14.150 | 1.00 | 33.99 | A |
| ATOM | 706 | CG   | PRO | 188 | -10.377 | 7.000  | -14.036 | 1.00 | 32.69 | A |
| ATOM | 707 | C    | PRO | 188 | -10.840 | 3.783  | -13.683 | 1.00 | 33.66 | A |
| ATOM | 708 | O    | PRO | 188 | -11.885 | 4.062  | -13.140 | 1.00 | 33.41 | A |
| ATOM | 709 | N    | PHE | 189 | -10.147 | 2.695  | -13.346 | 1.00 | 28.66 | A |
| ATOM | 710 | H    | PHE | 189 | -9.260  | 2.508  | -13.748 | 1.00 | 15.00 | A |
| ATOM | 711 | CA   | PHE | 189 | -10.721 | 2.013  | -12.171 | 1.00 | 26.71 | A |
| ATOM | 712 | CB   | PHE | 189 | -10.122 | 0.601  | -12.034 | 1.00 | 26.21 | A |
| ATOM | 713 | CG   | PHE | 189 | -10.671 | -0.189 | -10.849 | 1.00 | 22.92 | A |
| ATOM | 714 | CD1  | PHE | 189 | -10.126 | 0.005  | -9.566  | 1.00 | 17.72 | A |
| ATOM | 715 | CD2  | PHE | 189 | -11.687 | -1.165 | -11.064 | 1.00 | 21.88 | A |
| ATOM | 716 | CE1  | PHE | 189 | -10.590 | -0.815 | -8.522  | 1.00 | 19.12 | A |
| ATOM | 717 | CE2  | PHE | 189 | -12.124 | -1.995 | -10.011 | 1.00 | 21.13 | A |
| ATOM | 718 | CZ   | PHE | 189 | -11.571 | -1.806 | -8.736  | 1.00 | 18.44 | A |
| ATOM | 719 | C    | PHE | 189 | -10.445 | 2.815  | -10.909 | 1.00 | 27.14 | A |

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| ATOM | 720 | O | PHE | 189 | -9.308 | 3.244 | -10.706 | 1.00 | 28.72 | A |
|------|-----|-----|-----|-----|--------|-------|---------|------|-------|---|
| ATOM | 721 | N | ILE | 190 | -11.468 | 2.964 | -10.071 | 1.00 | 24.71 | A |
| ATOM | 722 | H | ILE | 190 | -12.408 | 2.786 | -10.388 | 1.00 | 15.00 | A |
| ATOM | 723 | CA | ILE | 190 | -11.193 | 3.626 | -8.788 | 1.00 | 24.03 | A |
| ATOM | 724 | CB | ILE | 190 | -11.316 | 5.242 | -8.743 | 1.00 | 26.86 | A |
| ATOM | 725 | CG2 | ILE | 190 | -11.892 | 5.979 | -9.997 | 1.00 | 19.87 | A |
| ATOM | 726 | CG1 | ILE | 190 | -11.801 | 5.888 | -7.424 | 1.00 | 22.54 | A |
| ATOM | 727 | CD1 | ILE | 190 | -12.819 | 7.012 | -7.645 | 1.00 | 28.56 | A |
| ATOM | 728 | C | ILE | 190 | -11.844 | 2.812 | -7.656 | 1.00 | 21.97 | A |
| ATOM | 729 | O | ILE | 190 | -12.891 | 2.197 | -7.801 | 1.00 | 16.30 | A |
| ATOM | 730 | N | ALA | 191 | -11.026 | 2.700 | -6.590 | 1.00 | 17.21 | A |
| ATOM | 731 | H | ALA | 191 | -10.124 | 3.124 | -6.662 | 1.00 | 15.00 | A |
| ATOM | 732 | CA | ALA | 191 | -11.501 | 2.195 | -5.321 | 1.00 | 15.20 | A |
| ATOM | 733 | CB | ALA | 191 | -10.730 | 0.928 | -4.968 | 1.00 | 14.79 | A |
| ATOM | 734 | C | ALA | 191 | -11.439 | 3.230 | -4.206 | 1.00 | 17.11 | A |
| ATOM | 735 | O | ALA | 191 | -10.467 | 3.961 | -4.052 | 1.00 | 14.04 | A |
| ATOM | 736 | N | SER | 192 | -12.511 | 3.245 | -3.433 | 1.00 | 14.72 | A |
| ATOM | 737 | H | SER | 192 | -13.277 | 2.694 | -3.804 | 1.00 | 15.00 | A |
| ATOM | 738 | CA | SER | 192 | -12.725 | 4.289 | -2.423 | 1.00 | 16.69 | A |
| ATOM | 739 | CB | SER | 192 | -13.931 | 5.144 | -2.803 | 1.00 | 14.83 | A |
| ATOM | 740 | OG | SER | 192 | -13.556 | 5.828 | -3.994 | 1.00 | 21.23 | A |
| ATOM | 741 | HG | SER | 192 | -14.367 | 5.966 | -4.520 | 1.00 | 15.00 | A |
| ATOM | 742 | C | SER | 192 | -12.980 | 3.682 | -1.069 | 1.00 | 17.77 | A |
| ATOM | 743 | O | SER | 192 | -13.753 | 2.738 | -0.947 | 1.00 | 20.76 | A |
| ATOM | 744 | N | LEU | 193 | -12.285 | 4.209 | -0.038 | 1.00 | 15.56 | A |
| ATOM | 745 | H | LEU | 193 | -11.681 | 4.959 | -0.280 | 1.00 | 15.00 | A |
| ATOM | 746 | CA | LEU | 193 | -12.510 | 3.761 | 1.366 | 1.00 | 13.27 | A |
| ATOM | 747 | CB | LEU | 193 | -11.195 | 3.825 | 2.217 | 1.00 | 12.74 | ·A |
| ATOM | 748 | CG | LEU | 193 | -11.051 | 3.141 | 3.604 | 1.00 | 14.37 | A |
| ATOM | 749 | CD1 | LEU | 193 | -12.272 | 2.354 | 4.116 | 1.00 | 14.67 | A |
| ATOM | 750 | CD2 | LEU | 193 | -10.274 | 3.986 | 4.622 | 1.00 | 12.64 | A |
| ATOM | 751 | C | LEU | 193 | -13.497 | 4.748 | 1.911 | 1.00 | 11.22 | A |
| ATOM | 752 | O | LEU | 193 | -13.188 | 5.912 | 1.903 | 1.00 | 12.22 | A |
| ATOM | 753 | N | CYS | 194 | -14.652 | 4.326 | 2.310 | 1.00 | 13.66 | A |
| ATOM | 754 | H | CYS | 194 | -14.828 | 3.347 | 2.276 | 1.00 | 15.00 | A |
| ATOM | 755 | CA | CYS | 194 | -15.595 | 5.360 | 2.713 | 1.00 | 14.84 | A |
| ATOM | 756 | CB | CYS | 194 | -16.915 | 5.409 | 1.918 | 1.00 | 17.58 | A |
| ATOM | 757 | SG | CYS | 194 | -16.623 | 5.417 | 0.165 | 1.00 | 16.33 | A |
| ATOM | 758 | C | CYS | 194 | -16.046 | 5.163 | 4.137 | 1.00 | 12.81 | A |
| ATOM | 759 | O | CYS | 194 | -15.983 | 4.072 | 4.655 | 1.00 | 10.34 | A |
| ATOM | 760 | N | LEU | 195 | -16.557 | 6.254 | 4.697 | 1.00 | 14.32 | A |
| ATOM | 761 | H | LEU | 195 | -16.541 | 7.088 | 4.154 | 1.00 | 15.00 | A |
| ATOM | 762 | CA | LEU | 195 | -17.039 | 6.291 | 6.076 | 1.00 | 14.89 | A |
| ATOM | 763 | CB | LEU | 195 | -16.195 | 7.372 | 6.789 | 1.00 | 15.56 | A |
| ATOM | 764 | CG | LEU | 195 | -16.571 | 7.680 | 8.242 | 1.00 | 15.56 | A |
| ATOM | 765 | CD1 | LEU | 195 | -15.932 | 8.967 | 8.762 | 1.00 | 13.72 | A |
| ATOM | 766 | CD2 | LEU | 195 | -16.463 | 6.448 | 9.154 | 1.00 | 17.25 | A |
| ATOM | 767 | C | LEU | 195 | -18.546 | 6.544 | 6.209 | 1.00 | 13.54 | A |
| ATOM | 768 | O | LEU | 195 | -19.038 | 7.521 | 5.705 | 1.00 | 14.56 | A |
| ATOM | 769 | N | LYS | 196 | -19.238 | 5.667 | 6.905 | 1.00 | 16.36 | A |
| ATOM | 770 | H | LYS | 196 | -18.719 | 4.875 | 7.197 | 1.00 | 15.00 | A |
| ATOM | 771 | CA | LYS | 196 | -20.577 | 5.972 | 7.405 | 1.00 | 21.01 | A |
| ATOM | 772 | CB | LYS | 196 | -21.475 | 4.726 | 7.146 | 1.00· | 22.66 | A |
| ATOM | 773 | CG | LYS | 196 | -22.953 | 4.839 | 7.590 | 1.00 | 31.25 | A |
| ATOM | 774 | CD | LYS | 196 | -23.364 | 4.915 | 9.104 | 1.00 | 40.25 | A |
| ATOM | 775 | CE | LYS | 196 | -23.189 | 3.694 | 10.060 | 1.00 | 43.56 | A |
| ATOM | 776 | NZ | LYS | 196 | -23.004 | 4.158 | 11.453· | 1.00 | 44.46 | A |
| ATOM | 777 | HZ1 | LYS | 196 | -22.182 | 4.799 | 11.467 | 1.00 | 15.00 | A |
| ATOM | 778 | HZ2 | LYS | 196 | -23.847 | 4.665 | 11.778 | 1.00 | 15.00 | A |
| ATOM | 779 | HZ3 | LYS | 196 | -22.807 | 3.334 | 12.066 | 1.00 | 15.00 | A |

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| ATOM | 780 | C | LYS | 196 | -20.478 | 6.290 | 8.899 | 1.00 | 19.25 | A |
|------|-----|------|------|-----|---------|--------|--------|------|-------|---|
| ATOM | 781 | O | LYS | 196 | -20.194 | 5.434 | 9.714 | 1.00 | 18.35 | A |
| ATOM | 782 | N | SER | 197 | -20.664 | 7.534 | 9.272 | 1.00 | 20.63 | A |
| ATOM | 783 | H | SER | 197 | -20.891 | 8.247 | 8.615 | 1.00 | 15.00 | A |
| ATOM | 784 | CA | SER | 197 | -20.752 | 7.701 | 10.729 | 1.00 | 24.87 | A |
| ATOM | 785 | CB | SER | 197 | -19.898 | 8.878 | 11.207 | 1.00 | 25.62 | A |
| ATOM | 786 | OG | SER | 197 | -19.563 | 8.687 | 12.588 | 1.00 | 32.22 | A |
| ATOM | 787 | HG | SER | 197 | -18.795 | 8.110 | 12.611 | 1.00 | 15.00 | A |
| ATOM | 788 | C | SER | 197 | -22.216 | 7.810 | 11.218 | 1.00 | 26.33 | A |
| ATOM | 789 | O | SER | 197 | -23.078 | 8.303 | 10.497 | 1.00 | 26.57 | A |
| ATOM | 790 | N | PRO | 198 | -22.534 | 7.274 | 12.407 | 1.00 | 26.77 | A |
| ATOM | 791 | CD | PRO | 198 | -21.649 | 6.526 | 13.301 | 1.00 | 32.92 | A |
| ATOM | 792 | CA | PRO | 198 | -23.919 | 7.381 | 12.913 | 1.00 | 28.73 | A |
| ATOM | 793 | CB | PRO | 198 | -23.784 | 6.789 | 14.318 | 1.00 | 32.89 | A |
| ATOM | 794 | CG | PRO | 198 | -22.289 | 6.726 | 14.659 | 1.00 | 33.55 | A |
| ATOM | 795 | C | PRO | 198 | -24.591 | 8.789 | 12.847 | 1.00 | 26.60 | A |
| ATOM | 796 | O | PRO | 198 | -24.035 | 9.817 | 13.242 | 1.00 | 20.20 | A |
| ATOM | 797 | N | GLY | 199 | -25.729 | 8.773 | 12.119 | 1.00 | 25.75 | A |
| ATOM | 798 | H | GLY | 199 | -26.170 | 7.857 | 12.057 | 1.00 | 15.00 | A |
| ATOM | 799 | CA | GLY | 199 | -26.486 | 10.003 | 11.790 | 1.00 | 26.91 | A |
| ATOM | 800 | C | GLY | 199 | -25.821 | 10.971 | 10.816 | 1.00 | 28.98 | A |
| ATOM | 801 | O | GLY | 199 | -26.084 | 12.151 | 10.797 | 1.00 | 31.05 | A |
| ATOM | 802 | N | ARG | 200 | -24.898 | 10.464 | 10.001 | 1.00 | 30.15 | A |
| ATOM | 803 | H | ARG | 200 | -24.629 | 9.519 | 10.165 | 1.00 | 15.00 | A |
| ATOM | 804 | CA | ARG | 200 | -24.140 | 11.384 | 9.166 | 1.00 | 28.98 | A |
| ATOM | 805 | CB | ARG | 200 | -22.749 | 11.590 | 9.783 | 1.00 | 33.16 | A |
| ATOM | 806 | CG | ARG | 200 | -22.739 | 12.290 | 11.162 | 1.00 | 38.34 | A |
| ATOM | 807 | CD | ARG | 200 | -21.327 | 12.530 | 11.705 | 1.00 | 42.14 | ·A |
| ATOM | 808 | NE | ARG | 200 | -21.292 | 12.875 | 13.131 | 1.00 | 43.64 | A |
| ATOM | 809 | HE | ARG | 200 | -21.327 | 13.831 | 13.424 | 1.00 | 15.00 | A |
| ATOM | 810 | CZ | ARG | 200 | -21.138 | 11.896 | 14.051 | 1.00 | 46.40 | A |
| ATOM | 811 | NH1 | ARG | 200 | -21.219 | 10.603 | 13.733 | 1.00 | 46.31 | A |
| ATOM | 812 | HH11 | ARG | 200 | -21.104 | 9.910 | 14.445 | 1.00 | 15.00 | A |
| ATOM | 813 | HH12 | ARG | 200 | -21.394 | 10.320 | 12.789 | 1.00 | 15.00 | A |
| ATOM | 814 | NH2 | ARG | 200 | -20.901 | 12.226 | 15.311 | 1.00 | 46.65 | A |
| ATOM | 815 | HH21 | ARG | 200 | -20.847 | 13.193 | 15.566 | 1.00 | 15.00 | A |
| ATOM | 816 | HH22 | ARG | 200 | -20.785 | 11.510 | 16.002 | 1.00 | 15.00 | A |
| ATOM | 817 | C | ARG | 200 | -24.084 | 10.967 | 7.710 | 1.00 | 27.77 | A |
| ATOM | 818 | O | ARG | 200 | -24.264 | 9.791 | 7.449 | 1.00 | 28.21 | A |
| ATOM | 819 | N | PHE | 201 | -23.853 | 11.926 | 6.792 | 1.00 | 30.83 | A |
| ATOM | 820 | H | PHE | 201 | -23.513 | 12.821 | 7.126 | 1.00 | 15.00 | A |
| ATOM | 821 | CA | PHE | 201 | -24.016 | 11.708 | 5.339 | 1.00 | 34.17 | A |
| ATOM | 822 | CB | PHE | 201 | -23.851 | 12.996 | 4.572 | 1.00 | 31.58 | A |
| ATOM | 823 | CG | PHE | 201 | -25.154 | 13.730 | 4.614 | 1.00 | 34.85 | A |
| ATOM | 824 | CD1 | PHE | 201 | -25.174 | 15.062 | 5.081 | 1.00 | 37.56 | A |
| ATOM | 825 | CD2 | PHE | 201 | -26.335 | 13.081 | 4.190 | 1.00 | 37.89 | A |
| ATOM | 826 | CE1 | PHE | 201 | -26.397 | 15.749 | 5.182 | 1.00 | 36.91 | A |
| ATOM | 827 | CE2 | PHE | 201 | -27.566 | 13.762 | 4.280 | 1.00 | 38.98 | A |
| ATOM | 828 | CZ | PHE | 201 | -27.572 | 15.065 | 4.815 | 1.00 | 37.61 | A |
| ATOM | 829 | C | PHE | 201 | -23.277 | 10.605 | 4.545 | 1.00 | 39.40 | A |
| ATOM | 830 | O | PHE | 201 | -23.853 | 10.034 | 3.604 | 1.00 | 45.71 | A |
| ATOM | 831 | N | GLU | 202 | -22.031 | 10.316 | 5.034 | 1.00 | 35.75 | A |
| ATOM | 832 | H | GLU | 202 | -21.878 | 10.753 | 5.925 | 1.00 | 15.00 | A |
| ATOM | 833 | CA | GLU | 202 | -20.964 | 9.564 | 4.318 | 1.00 | 34.52 | A |
| ATOM | 834 | CB | GLU | 202 | -21.295 | 8.540 | 3.234 | 1.00 | 33.66 | A |
| ATOM | 835 | CG | GLU | 202 | -21.924 | 7.245 | 3.713 | 1.00 | 40.61 | A |
| ATOM | 836 | CD | GLU | 202 | -22.647 | 6.505 | 2.561 | 1.00 | 46.12 | A |
| ATOM | 837 | OE1 | GLU | 202 | -23.461 | 5.613 | 2.886 | 1.00 | 46.89 | A |
| ATOM | 838 | OE2 | GLU | 202 | -22.417 | 6.814 | 1.370 | 1.00 | 45.63 | A |
| ATOM | 839 | C | GLU | 202 | -19.924 | 10.450 | 3.717 | 1.00 | 29.99 | A |

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| ATOM | 840 | O    | GLU | 202 | -20.137 | 11.567 | 3.300  | 1.00 | 30.76 | A |
|------|-----|------|-----|-----|---------|--------|--------|------|-------|---|
| ATOM | 841 | N    | ARG | 203 | -18.728 | 9.897  | 3.856  | 1.00 | 26.88 | A |
| ATOM | 842 | H    | ARG | 203 | -18.690 | 8.998  | 4.285  | 1.00 | 15.00 | A |
| ATOM | 843 | CA   | ARG | 203 | -17.539 | 10.603 | 3.358  | 1.00 | 21.88 | A |
| ATOM | 844 | CB   | ARG | 203 | -16.819 | 11.410 | 4.457  | 1.00 | 27.07 | A |
| ATOM | 845 | CG   | ARG | 203 | -17.681 | 12.187 | 5.467  | 1.00 | 37.32 | A |
| ATOM | 846 | CD   | ARG | 203 | -16.894 | 13.213 | 6.339  | 1.00 | 48.09 | A |
| ATOM | 847 | NE   | ARG | 203 | -15.911 | 12.667 | 7.308  | 1.00 | 56.90 | A |
| ATOM | 848 | HE   | ARG | 203 | -16.240 | 12.433 | 8.223  | 1.00 | 15.00 | A |
| ATOM | 849 | CZ   | ARG | 203 | -14.572 | 12.475 | 7.001  | 1.00 | 66.77 | A |
| ATOM | 850 | NH1  | ARG | 203 | -13.702 | 12.002 | 7.911  | 1.00 | 68.44 | A |
| ATOM | 851 | HH11 | ARG | 203 | -12.745 | 11.829 | 7.666  | 1.00 | 15.00 | A |
| ATOM | 852 | HH12 | ARG | 203 | -14.016 | 11.822 | 8.845  | 1.00 | 15.00 | A |
| ATOM | 853 | NH2  | ARG | 203 | -14.084 | 12.716 | 5.766  | 1.00 | 67.68 | A |
| ATOM | 854 | HH21 | ARG | 203 | -14.670 | 13.108 | 5.060  | 1.00 | 15.00 | A |
| ATOM | 855 | HH22 | ARG | 203 | -13.143 | 12.499 | 5.544  | 1.00 | 15.00 | A |
| ATOM | 856 | C    | ARG | 203 | -16.517 | 9.633  | 2.678  | 1.00 | 17.71 | A |
| ATOM | 857 | O    | ARG | 203 | -16.375 | 8.418  | 2.931  | 1.00 | 7.69  | A |
| ATOM | 858 | N    | ILE | 204 | -15.789 | 10.253 | 1.791  | 1.00 | 14.42 | A |
| ATOM | 859 | H    | ILE | 204 | -15.915 | 11.228 | 1.561  | 1.00 | 15.00 | A |
| ATOM | 860 | CA   | ILE | 204 | -14.662 | 9.482  | 1.353  | 1.00 | 18.32 | A |
| ATOM | 861 | CB   | ILE | 204 | -14.520 | 9.392  | -0.231 | 1.00 | 24.52 | A |
| ATOM | 862 | CG2  | ILE | 204 | -15.820 | 9.529  | -1.069 | 1.00 | 21.85 | A |
| ATOM | 863 | CG1  | ILE | 204 | -13.439 | 10.195 | -0.949 | 1.00 | 26.35 | A |
| ATOM | 864 | CD1  | ILE | 204 | -13.992 | 11.231 | -1.961 | 1.00 | 36.33 | A |
| ATOM | 865 | C    | ILE | 204 | -13.387 | 9.819  | 2.153  | 1.00 | 16.58 | A |
| ATOM | 866 | O    | ILE | 204 | -13.070 | 10.956 | 2.457  | 1.00 | 18.63 | A |
| ATOM | 867 | N    | LEU | 205 | -12.718 | 8.725  | 2.571  | 1.00 | 13.32 | A |
| ATOM | 868 | H    | LEU | 205 | -13.142 | 7.853  | 2.321  | 1.00 | 15.00 | A |
| ATOM | 869 | CA   | LEU | 205 | -11.467 | 8.829  | 3.322  | 1.00 | 10.01 | A |
| ATOM | 870 | CB   | LEU | 205 | -11.440 | 7.688  | 4.382  | 1.00 | 6.66  | A |
| ATOM | 871 | CG   | LEU | 205 | -12.571 | 7.727  | 5.441  | 1.00 | 7.99  | A |
| ATOM | 872 | CD1  | LEU | 205 | -12.722 | 9.088  | 6.089  | 1.00 | 8.78  | A |
| ATOM | 873 | CD2  | LEU | 205 | -12.419 | 6.720  | 6.582  | 1.00 | 8.08  | A |
| ATOM | 874 | C    | LEU | 205 | -10.268 | 8.811  | 2.377  | 1.00 | 9.75  | A |
| ATOM | 875 | O    | LEU | 205 | -9.416  | 9.655  | 2.320  | 1.00 | 10.25 | A |
| ATOM | 876 | N    | LEU | 206 | -10.252 | 7.769  | 1.562  | 1.00 | 10.28 | A |
| ATOM | 877 | H    | LEU | 206 | -10.991 | 7.119  | 1.684  | 1.00 | 15.00 | A |
| ATOM | 878 | CA   | LEU | 206 | -9.166  | 7.555  | 0.610  | 1.00 | 10.02 | A |
| ATOM | 879 | CB   | LEU | 206 | -8.249  | 6.384  | 0.990  | 1.00 | 11.94 | A |
| ATOM | 880 | CG   | LEU | 206 | -7.001  | 6.527  | 1.859  | 1.00 | 14.40 | A |
| ATOM | 881 | CD1  | LEU | 206 | -7.094  | 5.595  | 3.074  | 1.00 | 14.49 | A |
| ATOM | 882 | CD2  | LEU | 206 | -6.531  | 7.958  | 2.151  | 1.00 | 8.78  | A |
| ATOM | 883 | C    | LEU | 206 | -9.756  | 7.071  | -0.697 | 1.00 | 11.91 | A |
| ATOM | 884 | O    | LEU | 206 | -10.792 | 6.406  | -0.778 | 1.00 | 10.67 | A |
| ATOM | 885 | N    | ARG | 207 | -9.005  | 7.428  | -1.720 | 1.00 | 8.06  | A |
| ATOM | 886 | H    | ARG | 207 | -8.196  | 7.992  | -1.553 | 1.00 | 15.00 | A |
| ATOM | 887 | CA   | ARG | 207 | -9.309  | 6.823  | -2.992 | 1.00 | 10.45 | A |
| ATOM | 888 | CB   | ARG | 207 | -9.974  | 7.790  | -3.904 | 1.00 | 8.71  | A |
| ATOM | 889 | CG   | ARG | 207 | -11.258 | 8.270  | -3.357 | 1.00 | 15.68 | A |
| ATOM | 890 | CD   | ARG | 207 | -11.652 | 9.459  | -4.163 | 1.00 | 22.25 | A |
| ATOM | 891 | NE   | ARG | 207 | -12.670 | 9.192  | -5.171 | 1.00 | 29.59 | A |
| ATOM | 892 | HE   | ARG | 207 | -13.115 | 8.300  | -5.249 | 1.00 | 15.00 | A |
| ATOM | 893 | CZ   | ARG | 207 | -13.063 | 10.272 | -5.919 | 1.00 | 40.09 | A |
| ATOM | 894 | NH1  | ARG | 207 | -12.482 | 11.498 | -5.813 | 1.00 | 36.32 | A |
| ATOM | 895 | HH11 | ARG | 207 | -12.813 | 12.246 | -6.391 | 1.00 | 15.00 | A |
| ATOM | 896 | HH12 | ARG | 207 | -11.737 | 11.651 | -5.165 | 1.00 | 15.00 | A |
| ATOM | 897 | NH2  | ARG | 207 | -14.067 | 10.111 | -6.773 | 1.00 | 40.86 | A |
| ATOM | 898 | HH21 | ARG | 207 | -14.392 | 10.877 | -7.329 | 1.00 | 15.00 | A |
| ATOM | 899 | HH22 | ARG | 207 | -14.498 | 9.207  | -6.853 | 1.00 | 15.00 | A |

| ATOM | 900 | C | ARG | 207 | -8.044 | 6.456 | -3.741 | 1.00 | 12.59 | A |
|------|-----|------|-----|-----|--------|--------|---------|------|-------|---|
| ATOM | 901 | O | ARG | 207 | -7.053 | 7.150 | -3.787 | 1.00 | 15.58 | A |
| ATOM | 902 | N | ALA | 208 | -8.096 | 5.358 | -4.465 | 1.00 | 17.06 | A |
| ATOM | 903 | H | ALA | 208 | -8.879 | 4.758 | -4.355 | 1.00 | 15.00 | A |
| ATOM | 904 | CA | ALA | 208 | -7.025 | 5.128 | -5.465 | 1.00 | 17.00 | A |
| ATOM | 905 | CB | ALA | 208 | -6.052 | 4.020 | -5.072 | 1.00 | 14.69 | A |
| ATOM | 906 | C | ALA | 208 | -7.544 | 4.830 | -6.854 | 1.00 | 20.46 | A |
| ATOM | 907 | O | ALA | 208 | -8.438 | 4.020 | -7.057 | 1.00 | 21.89 | A |
| ATOM | 908 | N | ALA | 209 | -6.986 | 5.586 | -7.808 | 1.00 | 26.22 | A |
| ATOM | 909 | H | ALA | 209 | -6.280 | 6.235 | -7.533 | 1.00 | 15.00 | A |
| ATOM | 910 | CA | ALA | 209 | -7.253 | 5.208 | -9.196 | 1.00 | 28.06 | A |
| ATOM | 911 | CB | ALA | 209 | -7.702 | 6.380 | -10.069 | 1.00 | 27.10 | A |
| ATOM | 912 | C | ALA | 209 | -6.075 | 4.461 | -9.832 | 1.00 | 32.54 | A |
| ATOM | 913 | O | ALA | 209 | -4.895 | 4.726 | -9.593 | 1.00 | 33.00 | A |
| ATOM | 914 | N | ASN | 210 | -6.502 | 3.491 | -10.634 | 1.00 | 32.11 | A |
| ATOM | 915 | H | ASN | 210 | -7.466 | 3.249 | -10.531 | 1.00 | 15.00 | A |
| ATOM | 916 | CA | ASN | 210 | -5.674 | 2.893 | -11.662 | 1.00 | 36.00 | A |
| ATOM | 917 | CB | ASN | 210 | -5.366 | 1.446 | -11.355 | 1.00 | 39.53 | A |
| ATOM | 918 | CG | ASN | 210 | -4.463 | 1.366 | -10.154 | 1.00 | 42.59 | A |
| ATOM | 919 | OD1 | ASN | 210 | -4.285 | 2.273 | -9.342 | 1.00 | 39.26 | A |
| ATOM | 920 | ND2 | ASN | 210 | -3.951 | 0.165 | -10.055 | 1.00 | 41.77 | A |
| ATOM | 921 | HD21 | ASN | 210 | -3.990 | -0.479 | -10.817 | 1.00 | 15.00 | A |
| ATOM | 922 | HD22 | ASN | 210 | -3.364 | -0.081 | -9.279 | 1.00 | 15.00 | A |
| ATOM | 923 | C | ASN | 210 | -6.299 | 2.931 | -13.043 | 1.00 | 36.95 | A |
| ATOM | 924 | O | ASN | 210 | -7.492 | 2.752 | -13.259 | 1.00 | 36.93 | A |
| ATOM | 925 | N | THR | 211 | -5.447 | 3.168 | -14.013 | 1.00 | 37.83 | A |
| ATOM | 926 | H | THR | 211 | -4.484 | 3.377 | -13.821 | 1.00 | 15.00 | A |
| ATOM | 927 | CA | THR | 211 | -6.119 | 3.224 | -15.314 | 1.00 | 41.27 | ·A |
| ATOM | 928 | CB | THR | 211 | -5.325 | 4.158 | -16.268 | 1.00 | 44.53 | A |
| ATOM | 929 | OG1 | THR | 211 | -6.076 | 4.506 | -17.438 | 1.00 | 49.34 | A |
| ATOM | 930 | HG1 | THR | 211 | -6.032 | 5.493 | -17.508 | 1.00 | 15.00 | A |
| ATOM | 931 | CG2 | THR | 211 | -3.926 | 3.604 | -16.581 | 1.00 | 46.08 | A |
| ATOM | 932 | C | THR | 211 | -6.434 | 1.833 | -15.878 | 1.00 | 39.17 | A |
| ATOM | 933 | O | THR | 211 | -5.822 | 0.863 | -15.475 | 1.00 | 36.48 | A |
| ATOM | 934 | N | HIS | 212 | -7.416 | 1.718 | -16.789 | 1.00 | 37.14 | A |
| ATOM | 935 | H | HIS | 212 | -8.106 | 2.438 | -16.878 | 1.00 | 15.00 | A |
| ATOM | 936 | CA | HIS | 212 | -7.294 | 0.454 | -17.529 | 1.00 | 33.23 | A |
| ATOM | 937 | CB | HIS | 212 | -8.680 | -0.012 | -18.082 | 1.00 | 27.73 | A |
| ATOM | 938 | CG | HIS | 212 | -9.856 | 0.060 | -17.111 | 1.00 | 24.58 | A |
| ATOM | 939 | ND1 | HIS | 212 | -10.862 | 0.967 | -17.161 | 1.00 | 24.59 | A |
| ATOM | 940 | HD1 | HIS | 212 | -11.000 | 1.702 | -17.794 | 1.00 | 15.00 | A |
| ATOM | 941 | CD2 | HIS | 212 | -10.049 | -0.723 | -15.985 | 1.00 | 20.65 | A |
| ATOM | 942 | NE2 | HIS | 212 | -11.154 | -0.265 | -15.383 | 1.00 | 24.01 | A |
| ATOM | 943 | CE1 | HIS | 212 | -11.665 | 0.780 | -16.092 | 1.00 | 17.59 | A |
| ATOM | 944 | C | HIS | 212 | -6.257 | 0.633 | -18.683 | 1.00 | 38.31 | A |
| ATOM | 945 | O | HIS | 212 | -5.363 | -0.132 | -18.923 | 1.00 | 33.92 | A |
| ATOM | 946 | N | SER | 213 | -6.444 | 1.737 | -19.443 | 1.00 | 46.63 | A |
| ATOM | 947 | H | SER | 213 | -7.156 | 2.323 | -19.055 | 1.00 | 15.00 | A |
| ATOM | 948 | CA | SER | 213 | -5.705 | 2.177 | -20.675 | 1.00 | 53.91 | A |
| ATOM | 949 | CB | SER | 213 | -4.272 | 2.704 | -20.400 | 1.00 | 52.61 | A |
| ATOM | 950 | OG | SER | 213 | -3.266 | 1.697 | -20.547 | 1.00 | 53.97 | A |
| ATOM | 951 | HG | SER | 213 | -3.363 | 1.064 | -19.823 | 1.00 | 15.00 | A |
| ATOM | 952 | C | SER | 213 | -5.844 | 1.508 | -22.097 | 1.00 | 60.03 | A |
| ATOM | 953 | O | SER | 213 | -5.005 | 0.811 | -22.682 | 1.00 | 61.19 | A |
| ATOM | 954 | N | SER | 214 | -7.043 | 1.803 | -22.686 | 1.00 | 64.96 | A |
| ATOM | 955 | H | SER | 214 | -7.705 | 2.322 | -22.146 | 1.00 | 15.00 | A |
| ATOM | 956 | CA | SER | 214 | -7.463 | 1.456 | -24.094 | 1.00 | 69.62 | A |
| ATOM | 957 | CB | SER | 214 | -8.727 | 2.218 | -24.495 | 1.00 | 67.82 | A |
| ATOM | 958 | OG | SER | 214 | -9.563 | 2.257 | -23.336 | 1.00 | 67.64 | A |
| ATOM | 959 | HG | SER | 214 | -10.468 | 2.398 | -23.623 | 1.00 | 15.00 | A |

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| ATOM | 960 | C | SER | 214 | -6.518 | 1.587 | -25.300 | 1.00 | 72.08 | A |
|------|------|------|------|------|--------|--------|---------|------|-------|---|
| ATOM | 961 | O | SER | 214 | -6.102 | 2.683 | -25.686 | 1.00 | 73.45 | A |
| ATOM | 962 | N | ALA | 215 | -6.175 | 0.409 | -25.899 | 1.00 | 73.38 | A |
| ATOM | 963 | H | ALA | 215 | -5.456 | 0.596 | -26.565 | 1.00 | 15.00 | A |
| ATOM | 964 | CA | ALA | 215 | -6.858 | -0.915 | -25.753 | 1.00 | 72.62 | A |
| ATOM | 965 | CB | ALA | 215 | -7.199 | -1.505 | -27.138 | 1.00 | 73.08 | A |
| ATOM | 966 | C | ALA | 215 | -6.331 | -2.148 | -24.983 | 1.00 | 72.11 | A |
| ATOM | 967 | O | ALA | 215 | -7.020 | -3.161 | -25.069 | 1.00 | 72.74 | A |
| ATOM | 968 | N | LYS | 216 | -5.153 | -2.076 | -24.282 | 1.00 | 70.17 | A |
| ATOM | 969 | H | LYS | 216 | -4.747 | -1.165 | -24.199 | 1.00 | 15.00 | A |
| ATOM | 970 | CA | LYS | 216 | -4.482 | -3.256 | -23.626 | 1.00 | 67.38 | A |
| ATOM | 971 | CB | LYS | 216 | -3.458 | -2.691 | -22.648 | 1.00 | 65.30 | A |
| ATOM | 972 | CG | LYS | 216 | -2.217 | -2.107 | -23.321 | 1.00 | 66.86 | A |
| ATOM | 973 | CD | LYS | 216 | -1.419 | -3.149 | -24.134 | 1.00 | 68.81 | A |
| ATOM | 974 | CE | LYS | 216 | -0.082 | -2.674 | -24.740 | 1.00 | 67.51 | A |
| ATOM | 975 | NZ | LYS | 216 | 0.483 | -3.722 | -25.598 | 1.00 | 67.80 | A |
| ATOM | 976 | HZ1 | LYS | 216 | 0.620 | -4.590 | -25.041 | 1.00 | 15.00 | A |
| ATOM | 977 | HZ2 | LYS | 216 | -0.168 | -3.914 | -26.385 | 1.00 | 15.00 | A |
| ATOM | 978 | HZ3 | LYS | 216 | 1.401 | -3.406 | -25.973 | 1.00 | 15.00 | A |
| ATOM | 979 | C | LYS | 216 | -5.321 | -4.441 | -22.993 | 1.00 | 66.99 | A |
| ATOM | 980 | O | LYS | 216 | -6.462 | -4.266 | -22.575 | 1.00 | 69.90 | A |
| ATOM | 981 | N | PRO | 217 | -4.835 | -5.724 | -22.952 | 1.00 | 65.06 | A |
| ATOM | 982 | CD | PRO | 217 | -3.525 | -6.262 | -23.308 | 1.00 | 67.91 | A |
| ATOM | 983 | CA | PRO | 217 | -5.792 | -6.827 | -22.626 | 1.00 | 62.80 | A |
| ATOM | 984 | CB | PRO | 217 | -5.285 | -8.004 | -23.464 | 1.00 | 64.33 | A |
| ATOM | 985 | CG | PRO | 217 | -3.755 | -7.799 | -23.338 | 1.00 | 69.63 | A |
| ATOM | 986 | C | PRO | 217 | -5.837 | -7.237 | -21.150 | 1.00 | 59.77 | A |
| ATOM | 987 | O | PRO | 217 | -4.747 | -7.318 | -20.589 | 1.00 | 58.81 | ·A |
| ATOM | 988 | N | CYS | 218 | -7.115 | -7.516 | -20.627 | 1.00 | 55.45 | A |
| ATOM | 989 | H | CYS | 218 | -7.874 | -7.287 | -21.233 | 1.00 | 15.00 | A |
| ATOM | 990 | CA | CYS | 218 | -7.433 | -7.929 | -19.210 | 1.00 | 46.55 | A |
| ATOM | 991 | CB | CYS | 218 | -8.105 | -9.289 | -19.079 | 1.00 | 44.69 | A |
| ATOM | 992 | SG | CYS | 218 | -8.855 | -9.822 | -17.460 | 1.00 | 43.11 | A |
| ATOM | 993 | C | CYS | 218 | -6.265 | -7.994 | -18.263 | 1.00 | 43.24 | A |
| ATOM | 994 | O | CYS | 218 | -5.720 | -9.026 | -17.959 | 1.00 | 44.68 | A |
| ATOM | 995 | N | GLY | 219 | -5.853 | -6.820 | -17.876 | 1.00 | 40.28 | A |
| ATOM | 996 | H | GLY | 219 | -6.328 | -5.961 | -18.059 | 1.00 | 15.00 | A |
| ATOM | 997 | CA | GLY | 219 | -4.659 | -6.828 | -17.070 | 1.00 | 36.27 | A |
| ATOM | 998 | C | GLY | 219 | -5.017 | -7.080 | -15.643 | 1.00 | 33.86 | A |
| ATOM | 999 | O | GLY | 219 | -5.906 | -6.452 | -15.097 | 1.00 | 34.90 | A |
| ATOM | 1000 | N | GLN | 220 | -4.313 | -7.996 | -15.023 | 1.00 | 33.15 | A |
| ATOM | 1001 | H | GLN | 220 | -3.835 | -8.684 | -15.580 | 1.00 | 15.00 | A |
| ATOM | 1002 | CA | GLN | 220 | -4.448 | -7.929 | -13.578 | 1.00 | 29.92 | A |
| ATOM | 1003 | CB | GLN | 220 | -4.298 | -9.282 | -12.936 | 1.00 | 27.81 | A |
| ATOM | 1004 | CG | GLN | 220 | -5.380 | -9.340 | -11.883 | 1.00 | 30.94 | A |
| ATOM | 1005 | CD | GLN | 220 | -5.285 | -10.631 | -11.132 | 1.00 | 36.37 | A |
| ATOM | 1006 | OE1 | GLN | 220 | -4.216 | -10.969 | -10.661 | 1.00 | 38.47 | A |
| ATOM | 1007 | NE2 | GLN | 220 | -6.425 | -11.296 | -10.977 | 1.00 | 37.61 | A |
| ATOM | 1008 | HE21 | GLN | 220 | -6.295 | -12.235 | -10.667 | 1.00 | 15.00 | A |
| ATOM | 1009 | HE22 | GLN | 220 | -7.373 | -11.036 | -11.200 | 1.00 | 15.00 | A |
| ATOM | 1010 | C | GLN | 220 | -3.666 | -6.845 | -12.859 | 1.00 | 27.48 | A |
| ATOM | 1011 | O | GLN | 220 | -2.461 | -6.694 | -12.999 | 1.00 | 27.61 | A |
| ATOM | 1012 | N | GLN | 221 | -4.438 | -6.040 | -12.110 | 1.00 | 25.10 | A |
| ATOM | 1013 | H | GLN | 221 | -5.433 | -6.174 | -12.143 | 1.00 | 15.00 | A |
| ATOM | 1014 | CA | GLN | 221 | -3.803 | -4.929 | -11.387 | 1.00 | 22.41 | A |
| ATOM | 1015 | CB | GLN | 221 | -4.077 | -3.528 | -11.949 | 1.00 | 22.12 | A |
| ATOM | 1016 | CG | GLN | 221 | -3.284 | -3.029 | -13.163 | 1.00 | 32.16 | A |
| ATOM | 1017 | CD | GLN | 221 | -3.795 | -1.637 | -13.405 | 1.00 | 34.69 | A |
| ATOM | 1018 | OE1 | GLN | 221 | -3.746 | -0.763 | -12.558 | 1.00 | 42.12 | A |
| ATOM | 1019 | NE2 | GLN | 221 | -4.648 | -1.507 | -14.398 | 1.00 | 34.93 | A |

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|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 1020 | HE21 | GLN | 221 | -4.981 | -2.187 | -15.042 | 1.00 | 15.00 | A |
| ATOM | 1021 | HE22 | GLN | 221 | -4.844 | -0.551 | -14.575 | 1.00 | 15.00 | A |
| ATOM | 1022 | C | GLN | 221 | -4.227 | -4.913 | -9.948 | 1.00 | 19.54 | A |
| ATOM | 1023 | O | GLN | 221 | -5.300 | -5.381 | -9.611 | 1.00 | 19.46 | A |
| ATOM | 1024 | N | SER | 222 | -3.374 | -4.330 | -9.123 | 1.00 | 18.12 | A |
| ATOM | 1025 | H | SER | 222 | -2.442 | -4.098 | -9.441 | 1.00 | 15.00 | A |
| ATOM | 1026 | CA | SER | 222 | -3.851 | -4.120 | -7.752 | 1.00 | 19.45 | A |
| ATOM | 1027 | CB | SER | 222 | -3.104 | -4.947 | -6.691 | 1.00 | 19.99 | A |
| ATOM | 1028 | OG | SER | 222 | -3.096 | -6.339 | -7.053 | 1.00 | 24.64 | A |
| ATOM | 1029 | HG | SER | 222 | -2.651 | -6.336 | -7.904 | 1.00 | 15.00 | A |
| ATOM | 1030 | C | SER | 222 | -3.731 | -2.688 | -7.330 | 1.00 | 24.09 | A |
| ATOM | 1031 | O | SER | 222 | -2.992 | -1.929 | -7.944 | 1.00 | 29.41 | A |
| ATOM | 1032 | N | ILE | 223 | -4.534 | -2.386 | -6.283 | 1.00 | 22.81 | A |
| ATOM | 1033 | H | ILE | 223 | -5.172 | -3.127 | -6.074 | 1.00 | 15.00 | A |
| ATOM | 1034 | CA | ILE | 223 | -4.567 | -1.122 | -5.530 | 1.00 | 21.06 | A |
| ATOM | 1035 | CB | ILE | 223 | -5.970 | -0.490 | -5.852 | 1.00 | 19.87 | A |
| ATOM | 1036 | CG2 | ILE | 223 | -6.564 | 0.315 | -4.673 | 1.00 | 16.59 | A |
| ATOM | 1037 | CG1 | ILE | 223 | -5.911 | 0.278 | -7.188 | 1.00 | 15.22 | A |
| ATOM | 1038 | CD1 | ILE | 223 | -7.229 | 0.868 | -7.709 | 1.00 | 20.54 | A |
| ATOM | 1039 | C | ILE | 223 | -4.367 | -1.446 | -4.007 | 1.00 | 21.62 | A |
| ATOM | 1040 | O | ILE | 223 | -5.098 | -2.269 | -3.444 | 1.00 | 19.58 | A |
| ATOM | 1041 | N | HIS | 224 | -3.429 | -0.767 | -3.340 | 1.00 | 19.73 | A |
| ATOM | 1042 | H | HIS | 224 | -2.794 | -0.230 | -3.899 | 1.00 | 15.00 | A |
| ATOM | 1043 | CA | HIS | 224 | -3.497 | -0.671 | -1.858 | 1.00 | 16.45 | A |
| ATOM | 1044 | CB | HIS | 224 | -2.164 | -1.183 | -1.227 | 1.00 | 18.74 | A |
| ATOM | 1045 | CG | HIS | 224 | -2.182 | -1.442 | 0.296 | 1.00 | 14.92 | A |
| ATOM | 1046 | ND1 | HIS | 224 | -2.479 | -2.628 | 0.882 | 1.00 | 15.33 | A |
| ATOM | 1047 | HD1 | HIS | 224 | -2.667 | -3.515 | 0.505 | 1.00 | 15.00 | ·A |
| ATOM | 1048 | CD2 | HIS | 224 | -1.964 | -0.524 | 1.310 | 1.00 | 13.79 | A |
| ATOM | 1049 | NE2 | HIS | 224 | -2.137 | -1.127 | 2.517 | 1.00 | 10.52 | A |
| ATOM | 1050 | CE1 | HIS | 224 | -2.458 | -2.411 | 2.232 | 1.00 | 11.70 | A |
| ATOM | 1051 | C | HIS | 224 | -3.914 | 0.699 | -1.284 | 1.00 | 15.18 | A |
| ATOM | 1052 | O | HIS | 224 | -3.338 | 1.732 | -1.520 | 1.00 | 14.36 | A |
| ATOM | 1053 | N | LEU | 225 | -4.970 | 0.673 | -0.468 | 1.00 | 16.85 | A |
| ATOM | 1054 | H | LEU | 225 | -5.317 | -0.238 | -0.252 | 1.00 | 15.00 | A |
| ATOM | 1055 | CA | LEU | 225 | -5.395 | 1.885 | 0.256 | 1.00 | 15.55 | A |
| ATOM | 1056 | CB | LEU | 225 | -6.927 | 2.082 | 0.208 | 1.00 | 17.15 | A |
| ATOM | 1057 | CG | LEU | 225 | -7.495 | 2.456 | -1.154 | 1.00 | 18.03 | A |
| ATOM | 1058 | CD1 | LEU | 225 | -6.792 | 3.659 | -1.774 | 1.00 | 19.34 | A |
| ATOM | 1059 | CD2 | LEU | 225 | -8.994 | 2.659 | -1.098 | 1.00 | 13.66 | A |
| ATOM | 1060 | C | LEU | 225 | -5.074 | 1.758 | 1.739 | 1.00 | 14.77 | A |
| ATOM | 1061 | O | LEU | 225 | -5.347 | 0.726 | 2.345 | 1.00 | 12.20 | A |
| ATOM | 1062 | N | GLY | 226 | -4.544 | 2.829 | 2.344 | 1.00 | 18.04 | A |
| ATOM | 1063 | H | GLY | 226 | -4.218 | 3.616 | 1.813 | 1.00 | 15.00 | A |
| ATOM | 1064 | CA | GLY | 226 | -4.541 | 2.833 | 3.841 | 1.00 | 18.37 | A |
| ATOM | 1065 | C | GLY | 226 | -4.193 | 4.171 | 4.544 | 1.00 | 17.08 | A |
| ATOM | 1066 | O | GLY | 226 | -3.389 | 4.906 | 4.055 | 1.00 | 13.75 | A |
| ATOM | 1067 | N | GLY | 227 | -4.781 | 4.457 | 5.725 | 1.00 | 16.30 | A |
| ATOM | 1068 | H | GLY | 227 | -5.434 | 3.771 | 6.036 | 1.00 | 15.00 | A |
| ATOM | 1069 | CA | GLY | 227 | -4.379 | 5.649 | 6.490 | 1.00 | 8.52 | A |
| ATOM | 1070 | C | GLY | 227 | -4.935 | 5.631 | 7.959 | 1.00 | 12.75 | A |
| ATOM | 1071 | O | GLY | 227 | -5.651 | 4.748 | 8.466 | 1.00 | 10.57 | A |
| ATOM | 1072 | N | VAL | 228 | -4.588 | 6.698 | 8.675 | 1.00 | 9.23 | A |
| ATOM | 1073 | H | VAL | 228 | -4.040 | 7.398 | 8.222 | 1.00 | 15.00 | A |
| ATOM | 1074 | CA | VAL | 228 | -5.110 | 6.818 | 10.067 | 1.00 | 11.74 | A |
| ATOM | 1075 | CB | VAL | 228 | -4.085 | 7.320 | 11.144 | 1.00 | 14.30 | A |
| ATOM | 1076 | CG1 | VAL | 228 | -2.830 | 6.445 | 11.333 | 1.00 | 10.73 | A |
| ATOM | 1077 | CG2 | VAL | 228 | -4.789 | 7.565 | 12.479 | 1.00 | 17.07 | A |
| ATOM | 1078 | C | VAL | 228 | -6.238 | 7.803 | 10.098 | 1.00 | 9.03 | A |
| ATOM | 1079 | O | VAL | 228 | -6.089 | 8.937 | 9.649 | 1.00 | 12.01 | A |

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| ATOM | 1080 | N    | PHE | 229 | -7.347  | 7.299  | 10.640 | 1.00 | 9.88  | A |
|------|------|------|-----|-----|---------|--------|--------|------|-------|---|
| ATOM | 1081 | H    | PHE | 229 | -7.329  | 6.332  | 10.922 | 1.00 | 15.00 | A |
| ATOM | 1082 | CA   | PHE | 229 | -8.566  | 8.106  | 10.772 | 1.00 | 11.18 | A |
| ATOM | 1083 | CB   | PHE | 229 | -9.578  | 7.687  | 9.686  | 1.00 | 8.01  | A |
| ATOM | 1084 | CG   | PHE | 229 | -9.063  | 7.912  | 8.233  | 1.00 | 8.40  | A |
| ATOM | 1085 | CD1  | PHE | 229 | -9.140  | 9.196  | 7.649  | 1.00 | 10.03 | A |
| ATOM | 1086 | CD2  | PHE | 229 | -8.433  | 6.883  | 7.517  | 1.00 | 6.57  | A |
| ATOM | 1087 | CE1  | PHE | 229 | -8.512  | 9.443  | 6.395  | 1.00 | 5.18  | A |
| ATOM | 1088 | CE2  | PHE | 229 | -7.771  | 7.128  | 6.282  | 1.00 | 4.26  | A |
| ATOM | 1089 | CZ   | PHE | 229 | -7.813  | 8.424  | 5.731  | 1.00 | 5.71  | A |
| ATOM | 1090 | C    | PHE | 229 | -9.202  | 8.014  | 12.197 | 1.00 | 14.39 | A |
| ATOM | 1091 | O    | PHE | 229 | -9.116  | 7.000  | 12.870 | 1.00 | 13.92 | A |
| ATOM | 1092 | N    | GLU | 230 | -9.863  | 9.064  | 12.672 | 1.00 | 17.93 | A |
| ATOM | 1093 | H    | GLU | 230 | -9.912  | 9.892  | 12.113 | 1.00 | 15.00 | A |
| ATOM | 1094 | CA   | GLU | 230 | -10.856 | 8.944  | 13.770 | 1.00 | 18.08 | A |
| ATOM | 1095 | CB   | GLU | 230 | -11.218 | 10.303 | 14.393 | 1.00 | 16.17 | A |
| ATOM | 1096 | CG   | GLU | 230 | -11.068 | 10.090 | 15.889 | 1.00 | 27.69 | A |
| ATOM | 1097 | CD   | GLU | 230 | -12.314 | 10.091 | 16.805 | 1.00 | 33.06 | A |
| ATOM | 1098 | OE1  | GLU | 230 | -13.355 | 10.707 | 16.552 | 1.00 | 38.26 | A |
| ATOM | 1099 | OE2  | GLU | 230 | -12.218 | 9.477  | 17.863 | 1.00 | 38.14 | A |
| ATOM | 1100 | C    | GLU | 230 | -12.225 | 8.268  | 13.453 | 1.00 | 18.70 | A |
| ATOM | 1101 | O    | GLU | 230 | -12.967 | 8.519  | 12.492 | 1.00 | 21.58 | A |
| ATOM | 1102 | N    | LEU | 231 | -12.542 | 7.334  | 14.361 | 1.00 | 13.79 | A |
| ATOM | 1103 | H    | LEU | 231 | -11.840 | 7.125  | 15.015 | 1.00 | 15.00 | A |
| ATOM | 1104 | CA   | LEU | 231 | -13.885 | 6.836  | 14.330 | 1.00 | 13.52 | A |
| ATOM | 1105 | CB   | LEU | 231 | -13.954 | 5.378  | 14.002 | 1.00 | 13.90 | A |
| ATOM | 1106 | CG   | LEU | 231 | -13.199 | 5.064  | 12.725 | 1.00 | 15.44 | A |
| ATOM | 1107 | CD1  | LEU | 231 | -13.781 | 5.712  | 11.436 | 1.00 | 10.24 | A |
| ATOM | 1108 | CD2  | LEU | 231 | -12.970 | 3.569  | 12.769 | 1.00 | 11.74 | A |
| ATOM | 1109 | C    | LEU | 231 | -14.638 | 7.074  | 15.591 | 1.00 | 14.88 | A |
| ATOM | 1110 | O    | LEU | 231 | -14.145 | 6.912  | 16.692 | 1.00 | 12.46 | A |
| ATOM | 1111 | N    | GLN | 232 | -15.891 | 7.411  | 15.350 | 1.00 | 19.40 | A |
| ATOM | 1112 | H    | GLN | 232 | -16.107 | 7.560  | 14.394 | 1.00 | 15.00 | A |
| ATOM | 1113 | CA   | GLN | 232 | -16.920 | 7.509  | 16.389 | 1.00 | 21.07 | A |
| ATOM | 1114 | CB   | GLN | 232 | -18.132 | 8.234  | 15.804 | 1.00 | 23.55 | A |
| ATOM | 1115 | CG   | GLN | 232 | -17.792 | 9.709  | 15.687 | 1.00 | 28.60 | A |
| ATOM | 1116 | CD   | GLN | 232 | -17.625 | 10.200 | 17.102 | 1.00 | 33.66 | A |
| ATOM | 1117 | OE1  | GLN | 232 | -18.623 | 10.472 | 17.742 | 1.00 | 38.08 | A |
| ATOM | 1118 | NE2  | GLN | 232 | -16.380 | 10.254 | 17.596 | 1.00 | 33.41 | A |
| ATOM | 1119 | HE21 | GLN | 232 | -15.596 | 10.186 | 16.972 | 1.00 | 15.00 | A |
| ATOM | 1120 | HE22 | GLN | 232 | -16.387 | 10.470 | 18.576 | 1.00 | 15.00 | A |
| ATOM | 1121 | C    | GLN | 232 | -17.402 | 6.148  | 16.851 | 1.00 | 21.86 | A |
| ATOM | 1122 | O    | GLN | 232 | -17.368 | 5.218  | 16.052 | 1.00 | 21.58 | A |
| ATOM | 1123 | N    | PRO | 233 | -17.906 | 6.013  | 18.115 | 1.00 | 22.31 | A |
| ATOM | 1124 | CD   | PRO | 233 | -17.962 | 7.033  | 19.168 | 1.00 | 21.41 | A |
| ATOM | 1125 | CA   | PRO | 233 | -18.570 | 4.747  | 18.442 | 1.00 | 21.21 | A |
| ATOM | 1126 | CB   | PRO | 233 | -19.013 | 4.987  | 19.866 | 1.00 | 23.88 | A |
| ATOM | 1127 | CG   | PRO | 233 | -18.661 | 6.404  | 20.339 | 1.00 | 20.95 | A |
| ATOM | 1128 | C    | PRO | 233 | -19.667 | 4.417  | 17.434 | 1.00 | 23.66 | A |
| ATOM | 1129 | O    | PRO | 233 | -20.275 | 5.319  | 16.875 | 1.00 | 26.89 | A |
| ATOM | 1130 | N    | GLY | 234 | -19.731 | 3.140  | 17.059 | 1.00 | 22.77 | A |
| ATOM | 1131 | H    | GLY | 234 | -19.082 | 2.466  | 17.417 | 1.00 | 15.00 | A |
| ATOM | 1132 | CA   | GLY | 234 | -20.766 | 2.767  | 16.072 | 1.00 | 19.45 | A |
| ATOM | 1133 | C    | GLY | 234 | -20.545 | 3.241  | 14.625 | 1.00 | 19.67 | A |
| ATOM | 1134 | O    | GLY | 234 | -21.299 | 2.980  | 13.715 | 1.00 | 23.81 | A |
| ATOM | 1135 | N    | ALA | 235 | -19.405 | 3.926  | 14.368 | 1.00 | 18.89 | A |
| ATOM | 1136 | H    | ALA | 235 | -19.096 | 4.485  | 15.135 | 1.00 | 15.00 | A |
| ATOM | 1137 | CA   | ALA | 235 | -18.431 | 3.515  | 13.296 | 1.00 | 22.17 | A |
| ATOM | 1138 | CB   | ALA | 235 | -18.193 | 2.042  | 13.039 | 1.00 | 6.68  | A |
| ATOM | 1139 | C    | ALA | 235 | -18.540 | 4.160  | 11.993 | 1.00 | 21.96 | A |

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|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 1140 | O | ALA | 235 | -18.486 | 5.385 | 12.100 | 1.00 | 26.42 | A |
| ATOM | 1141 | N | SER | 236 | -18.699 | 3.498 | 10.787 | 1.00 | 20.94 | A |
| ATOM | 1142 | H | SER | 236 | -18.824 | 4.326 | 10.254 | 1.00 | 15.00 | A |
| ATOM | 1143 | CA | SER | 236 | -18.630 | 2.227 | 9.961 | 1.00 | 17.60 | A |
| ATOM | 1144 | CB | SER | 236 | -19.905 | 1.876 | 9.160 | 1.00 | 14.98 | A |
| ATOM | 1145 | OG | SER | 236 | -20.662 | 0.908 | 9.833 | 1.00 | 21.35 | A |
| ATOM | 1146 | HG | SER | 236 | -21.599 | 0.910 | 9.647 | 1.00 | 15.00 | A |
| ATOM | 1147 | C | SER | 236 | -17.794 | 2.538 | 8.714 | 1.00 | 13.65 | A |
| ATOM | 1148 | O | SER | 236 | -17.939 | 3.614 | 8.131 | 1.00 | 16.29 | A |
| ATOM | 1149 | N | VAL | 237 | -16.986 | 1.567 | 8.286 | 1.00 | 14.95 | A |
| ATOM | 1150 | H | VAL | 237 | -16.764 | 0.823 | 8.949 | 1.00 | 15.00 | A |
| ATOM | 1151 | CA | VAL | 237 | -16.201 | 1.802 | 7.077 | 1.00 | 11.42 | A |
| ATOM | 1152 | CB | VAL | 237 | -14.681 | 2.004 | 7.284 | 1.00 | 12.49 | A |
| ATOM | 1153 | CG1 | VAL | 237 | -14.113 | 0.726 | 7.939 | 1.00 | 13.10 | A |
| ATOM | 1154 | CG2 | VAL | 237 | -14.254 | 3.396 | 7.846 | 1.00 | 10.27 | A |
| ATOM | 1155 | C | VAL | 237 | -16.468 | 0.746 | 6.035 | 1.00 | 8.76 | A |
| ATOM | 1156 | O | VAL | 237 | -16.827 | -0.363 | 6.341 | 1.00 | 12.84 | A |
| ATOM | 1157 | N | PHE | 238 | -16.354 | 1.158 | 4.773 | 1.00 | 12.45 | A |
| ATOM | 1158 | H | PHE | 238 | -16.139 | 2.128 | 4.652 | 1.00 | 15.00 | A |
| ATOM | 1159 | CA | PHE | 238 | -16.521 | 0.213 | 3.653 | 1.00 | 11.21 | A |
| ATOM | 1160 | CB | PHE | 238 | -18.013 | 0.137 | 3.322 | 1.00 | 13.00 | A |
| ATOM | 1161 | CG | PHE | 238 | -18.634 | 1.468 | 2.899 | 1.00 | 12.17 | A |
| ATOM | 1162 | CD1 | PHE | 238 | -18.763 | 1.812 | 1.518 | 1.00 | 12.94 | A |
| ATOM | 1163 | CD2 | PHE | 238 | -19.135 | 2.332 | 3.887 | 1.00 | 10.55 | A |
| ATOM | 1164 | CE1 | PHE | 238 | -19.407 | 3.010 | 1.092 | 1.00 | 14.01 | A |
| ATOM | 1165 | CE2 | PHE | 238 | -19.786 | 3.504 | 3.470 | 1.00 | 12.74 | A |
| ATOM | 1166 | CZ | PHE | 238 | -19.917 | 3.836 | 2.100 | 1.00 | 13.17 | A |
| ATOM | 1167 | C | PHE | 238 | -15.725 | 0.582 | 2.379 | 1.00 | 11.20 | ·A |
| ATOM | 1168 | O | PHE | 238 | -15.137 | 1.638 | 2.267 | 1.00 | 8.73 | A |
| ATOM | 1169 | N | VAL | 239 | -15.726 | -0.300 | 1.383 | 1.00 | 14.34 | A |
| ATOM | 1170 | H | VAL | 239 | -16.187 | -1.170 | 1.523 | 1.00 | 15.00 | A |
| ATOM | 1171 | CA | VAL | 239 | -14.982 | 0.027 | 0.154 | 1.00 | 14.65 | A |
| ATOM | 1172 | CB | VAL | 239 | -13.900 | -1.043 | -0.162 | 1.00 | 14.09 | A |
| ATOM | 1173 | CG1 | VAL | 239 | -13.004 | -1.318 | 1.038 | 1.00 | 14.55 | A |
| ATOM | 1174 | CG2 | VAL | 239 | -13.064 | -0.594 | -1.361 | 1.00 | 14.74 | A |
| ATOM | 1175 | C | VAL | 239 | -15.930 | 0.081 | -1.043 | 1.00 | 18.32 | A |
| ATOM | 1176 | O | VAL | 239 | -16.558 | -0.903 | -1.369 | 1.00 | 18.99 | A |
| ATOM | 1177 | N | ASN | 240 | -16.000 | 1.207 | -1.707 | 1.00 | 19.26 | A |
| ATOM | 1178 | H | ASN | 240 | -15.420 | 1.947 | -1.383 | 1.00 | 15.00 | A |
| ATOM | 1179 | CA | ASN | 240 | -16.613 | 1.355 | -3.031 | 1.00 | 21.66 | A |
| ATOM | 1180 | CB | ASN | 240 | -16.850 | 2.856 | -3.095 | 1.00 | 24.58 | A |
| ATOM | 1181 | CG | ASN | 240 | -18.167 | 3.077 | -3.708 | 1.00 | 29.09 | A |
| ATOM | 1182 | OD1 | ASN | 240 | -18.948 | 2.123 | -3.740 | 1.00 | 35.44 | A |
| ATOM | 1183 | ND2 | ASN | 240 | -18.293 | 4.331 | -4.166 | 1.00 | 34.71 | A |
| ATOM | 1184 | HD21 | ASN | 240 | -19.149 | 4.489 | -4.657 | 1.00 | 15.00 | A |
| ATOM | 1185 | C | ASN | 240 | -15.669 | 0.950 | -4.184 | 1.00 | 20.96 | A |
| ATOM | 1186 | O | ASN | 240 | -14.473 | 1.128 | -4.058 | 1.00 | 20.99 | A |
| ATOM | 1187 | N | VAL | 241 | -16.189 | 0.383 | -5.275 | 1.00 | 21.52 | A |
| ATOM | 1188 | H | VAL | 241 | -17.182 | 0.230 | -5.295 | 1.00 | 15.00 | A |
| ATOM | 1189 | CA | VAL | 241 | -15.387 | 0.439 | -6.516 | 1.00 | 20.56 | A |
| ATOM | 1190 | CB | VAL | 241 | -14.581 | -0.850 | -6.849 | 1.00 | 18.02 | A |
| ATOM | 1191 | CG1 | VAL | 241 | -15.501 | -2.058 | -7.063 | 1.00 | 15.06 | A |
| ATOM | 1192 | CG2 | VAL | 241 | -13.597 | -1.259 | -5.764 | 1.00 | 20.05 | A |
| ATOM | 1193 | C | VAL | 241 | -16.253 | 0.758 | -7.741 | 1.00 | 18.88 | A |
| ATOM | 1194 | O | VAL | 241 | -17.441 | 0.500 | -7.819 | 1.00 | 18.63 | A |
| ATOM | 1195 | N | THR | 242 | -15.541 | 1.162 | -8.762 | 1.00 | 21.24 | A |
| ATOM | 1196 | H | THR | 242 | -14.704 | 1.653 | -8.486 | 1.00 | 15.00 | A |
| ATOM | 1197 | CA | THR | 242 | -16.246 | 1.476 | -10.031 | 1.00 | 20.63 | A |
| ATOM | 1198 | CB | THR | 242 | -15.342 | 2.269 | -10.981 | 1.00 | 15.80 | A |
| ATOM | 1199 | OG1 | THR | 242 | -14.035 | 1.663 | -10.953 | 1.00 | 17.72 | A |

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| ATOM | 1200 | HG1 | THR | 242 | -13.721 | 1.969 | -11.812 | 1.00 | 15.00 | A |
|------|------|-----|-----|-----|---------|-------|---------|------|-------|---|
| ATOM | 1201 | CG2 | THR | 242 | -15.238 | 3.732 | -10.650 | 1.00 | 15.04 | A |
| ATOM | 1202 | C | THR | 242 | -16.755 | 0.240 | -10.783 | 1.00 | 18.92 | A |
| ATOM | 1203 | O | THR | 242 | -17.846 | 0.198 | -11.297 | 1.00 | 21.26 | A |
| ATOM | 1204 | N | ASP | 243 | -15.923 | -0.806 | -10.718 | 1.00 | 20.98 | A |
| ATOM | 1205 | H | ASP | 243 | -15.087 | -0.580 | -10.221 | 1.00 | 15.00 | A |
| ATOM | 1206 | CA | ASP | 243 | -16.092 | -1.977 | -11.628 | 1.00 | 21.28 | A |
| ATOM | 1207 | CB | ASP | 243 | -14.905 | -2.126 | -12.594 | 1.00 | 22.05 | A |
| ATOM | 1208 | CG | ASP | 243 | -14.932 | -0.954 | -13.492 | 1.00 | 28.23 | A |
| ATOM | 1209 | OD1 | ASP | 243 | -14.314 | 0.051 | -13.115 | 1.00 | 28.43 | A |
| ATOM | 1210 | OD2 | ASP | 243 | -15.588 | -1.033 | -14.535 | 1.00 | 33.00 | A |
| ATOM | 1211 | C | ASP | 243 | -16.123 | -3.308 | -10.923 | 1.00 | 20.38 | A |
| ATOM | 1212 | O | ASP | 243 | -15.148 | -4.072 | -10.967 | 1.00 | 20.43 | A |
| ATOM | 1213 | N | PRO | 244 | -17.204 | -3.553 | -10.154 | 1.00 | 19.92 | A |
| ATOM | 1214 | CD | PRO | 244 | -18.481 | -2.871 | -10.071 | 1.00 | 16.83 | A |
| ATOM | 1215 | CA | PRO | 244 | -17.120 | -4.706 | -9.269 | 1.00 | 19.13 | A |
| ATOM | 1216 | CB | PRO | 244 | -18.293 | -4.535 | -8.275 | 1.00 | 15.33 | A |
| ATOM | 1217 | CG | PRO | 244 | -18.890 | -3.174 | -8.634 | 1.00 | 15.21 | A |
| ATOM | 1218 | C | PRO | 244 | -16.975 | -6.034 | -9.974 | 1.00 | 19.29 | A |
| ATOM | 1219 | O | PRO | 244 | -16.194 | -6.859 | -9.548 | 1.00 | 23.48 | A |
| ATOM | 1220 | N | SER | 245 | -17.581 | -6.163 | -11.150 | 1.00 | 22.60 | A |
| ATOM | 1221 | H | SER | 245 | -18.220 | -5.459 | -11.473 | 1.00 | 15.00 | A |
| ATOM | 1222 | CA | SER | 245 | -17.414 | -7.429 | -11.942 | 1.00 | 25.50 | A |
| ATOM | 1223 | CB | SER | 245 | -18.256 | -7.369 | -13.234 | 1.00 | 21.36 | A |
| ATOM | 1224 | OG | SER | 245 | -19.667 | -7.567 | -12.981 | 1.00 | 38.26 | A |
| ATOM | 1225 | HG | SER | 245 | -19.848 | -7.390 | -12.038 | 1.00 | 15.00 | A |
| ATOM | 1226 | C | SER | 245 | -15.955 | -7.776 | -12.328 | 1.00 | 24.14 | A |
| ATOM | 1227 | O | SER | 245 | -15.477 | -8.859 | -12.623 | 1.00 | 24.84 | ·A |
| ATOM | 1228 | N | GLN | 246 | -15.177 | -6.689 | -12.385 | 1.00 | 28.52 | A |
| ATOM | 1229 | H | GLN | 246 | -15.638 | -5.804 | -12.265 | 1.00 | 15.00 | A |
| ATOM | 1230 | CA | GLN | 246 | -13.743 | -6.923 | -12.590 | 1.00 | 26.45 | A |
| ATOM | 1231 | CB | GLN | 246 | -13.144 | -5.645 | -13.233 | 1.00 | 29.90 | A |
| ATOM | 1232 | CG | GLN | 246 | -13.403 | -5.435 | -14.758 | 1.00 | 26.84 | A |
| ATOM | 1233 | CD | GLN | 246 | -14.862 | -5.341 | -15.129 | 1.00 | 21.60 | A |
| ATOM | 1234 | OE1 | GLN | 246 | -15.538 | -4.503 | -14.616 | 1.00 | 24.20 | A |
| ATOM | 1235 | NE2 | GLN | 246 | -15.334 | -6.234 | -15.975 | 1.00 | 26.15 | A |
| ATOM | 1236 | HE21 | GLN | 246 | -14.763 | -6.924 | -16.423 | 1.00 | 15.00 | A |
| ATOM | 1237 | HE22 | GLN | 246 | -16.320 | -6.119 | -16.084 | 1.00 | 15.00 | A |
| ATOM | 1238 | C | GLN | 246 | -12.936 | -7.372 | -11.363 | 1.00 | 27.14 | A |
| ATOM | 1239 | O | GLN | 246 | -11.721 | -7.570 | -11.454 | 1.00 | 25.73 | A |
| ATOM | 1240 | N | VAL | 247 | -13.615 | -7.395 | -10.196 | 1.00 | 23.70 | A |
| ATOM | 1241 | H | VAL | 247 | -14.600 | -7.594 | -10.146 | 1.00 | 15.00 | A |
| ATOM | 1242 | CA | VAL | 247 | -12.728 | -7.569 | -9.097 | 1.00 | 21.91 | A |
| ATOM | 1243 | CB | VAL | 247 | -13.156 | -6.814 | -7.859 | 1.00 | 21.59 | A |
| ATOM | 1244 | CG1 | VAL | 247 | -14.027 | -7.616 | -6.962 | 1.00 | 24.52 | A |
| ATOM | 1245 | CG2 | VAL | 247 | -13.680 | -5.409 | -8.167 | 1.00 | 21.61 | A |
| ATOM | 1246 | C | VAL | 247 | -12.258 | -8.998 | -8.910 | 1.00 | 21.55 | A |
| ATOM | 1247 | O | VAL | 247 | -12.946 | -9.912 | -9.251 | 1.00 | 19.53 | A |
| ATOM | 1248 | N | SER | 248 | -11.000 | -9.152 | -8.444 | 1.00 | 21.31 | A |
| ATOM | 1249 | H | SER | 248 | -10.558 | -8.342 | -8.070 | 1.00 | 15.00 | A |
| ATOM | 1250 | CA | SER | 248 | -10.414 | -10.499 | -8.327 | 1.00 | 21.97 | A |
| ATOM | 1251 | CB | SER | 248 | -8.939 | -10.571 | -8.828 | 1.00 | 23.61 | A |
| ATOM | 1252 | OG | SER | 248 | -8.860 | -9.952 | -10.128 | 1.00 | 20.21 | A |
| ATOM | 1253 | HG | SER | 248 | -9.752 | -10.027 | -10.496 | 1.00 | 15.00 | A |
| ATOM | 1254 | C | SER | 248 | -10.538 | -11.076 | -6.946 | 1.00 | 19.28 | A |
| ATOM | 1255 | O | SER | 248 | -10.048 | -10.409 | -6.052 | 1.00 | 20.64 | A |
| ATOM | 1256 | N | HIS | 249 | -11.269 | -12.204 | -6.814 | 1.00 | 18.72 | A |
| ATOM | 1257 | H | HIS | 249 | -11.284 | -12.753 | -7.674 | 1.00 | 15.00 | A |
| ATOM | 1258 | CA | HIS | 249 | -11.640 | -12.673 | -5.478 | 1.00 | 17.22 | A |
| ATOM | 1259 | CB | HIS | 249 | -13.080 | -13.152 | -5.484 | 1.00 | 13.10 | A |

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| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 1260 | CG | HIS | 249 | -13.919 | -11.905 | -5.550 | 1.00 | 10.13 | A |
| ATOM | 1261 | ND1 | HIS | 249 | -14.137 | -11.129 | -4.486 | 1.00 | 13.47 | A |
| ATOM | 1262 | HD1 | HIS | 249 | -13.720 | -11.294 | -3.611 | 1.00 | 15.00 | A |
| ATOM | 1263 | CD2 | HIS | 249 | -14.662 | -11.414 | -6.610 | 1.00 | 10.62 | A |
| ATOM | 1264 | NE2 | HIS | 249 | -15.317 | -10.347 | -6.134 | 1.00 | 15.51 | A |
| ATOM | 1265 | CE1 | HIS | 249 | -15.018 | -10.142 | -4.821 | 1.00 | 12.36 | A |
| ATOM | 1266 | C | HIS | 249 | -10.701 | -13.683 | -4.858 | 1.00 | 23.58 | A |
| ATOM | 1267 | O | HIS | 249 | -11.103 | -14.729 | -4.359 | 1.00 | 21.98 | A |
| ATOM | 1268 | N | GLY | 250 | -9.398 | -13.258 | -4.878 | 1.00 | 29.10 | A |
| ATOM | 1269 | H | GLY | 250 | -9.252 | -12.351 | -5.253 | 1.00 | 15.00 | A |
| ATOM | 1270 | CA | GLY | 250 | -8.410 | -14.041 | -4.115 | 1.00 | 24.27 | A |
| ATOM | 1271 | C | GLY | 250 | -8.336 | -15.372 | -4.743 | 1.00 | 25.93 | A |
| ATOM | 1272 | O | GLY | 250 | -8.940 | -15.520 | -5.795 | 1.00 | 29.26 | A |
| ATOM | 1273 | N | THR | 251 | -7.594 | -16.302 | -4.127 | 1.00 | 22.38 | A |
| ATOM | 1274 | H | THR | 251 | -7.485 | -17.038 | -4.804 | 1.00 | 15.00 | A |
| ATOM | 1275 | CA | THR | 251 | -7.111 | -16.139 | -2.725 | 1.00 | 21.12 | A |
| ATOM | 1276 | CB | THR | 251 | -6.988 | -17.525 | -1.933 | 1.00 | 24.76 | A |
| ATOM | 1277 | OG1 | THR | 251 | -5.877 | -17.641 | -0.981 | 1.00 | 22.90 | A |
| ATOM | 1278 | HG1 | THR | 251 | -6.063 | -18.366 | -0.381 | 1.00 | 15.00 | A |
| ATOM | 1279 | CG2 | THR | 251 | -6.968 | -18.722 | -2.890 | 1.00 | 22.77 | A |
| ATOM | 1280 | C | THR | 251 | -5.952 | -15.158 | -2.473 | 1.00 | 17.96 | A |
| ATOM | 1281 | O | THR | 251 | -4.969 | -15.043 | -3.213 | 1.00 | 12.30 | A |
| ATOM | 1282 | N | GLY | 252 | -6.241 | -14.367 | -1.419 | 1.00 | 16.85 | A |
| ATOM | 1283 | H | GLY | 252 | -7.093 | -14.432 | -0.862 | 1.00 | 15.00 | A |
| ATOM | 1284 | CA | GLY | 252 | -5.277 | -13.375 | -0.928 | 1.00 | 13.16 | A |
| ATOM | 1285 | C | GLY | 252 | -5.357 | -12.058 | -1.670 | 1.00 | 15.51 | A |
| ATOM | 1286 | O | GLY | 252 | -4.580 | -11.168 | -1.439 | 1.00 | 15.18 | A |
| ATOM | 1287 | N | PHE | 253 | -6.189 | -12.063 | -2.744 | 1.00 | 16.66 | A |
| ATOM | 1288 | H | PHE | 253 | -6.868 | -12.805 | -2.761 | 1.00 | 15.00 | A |
| ATOM | 1289 | CA | PHE | 253 | -6.110 | -10.892 | -3.651 | 1.00 | 15.77 | A |
| ATOM | 1290 | CB | PHE | 253 | -6.649 | -11.216 | -5.100 | 1.00 | 17.11 | A |
| ATOM | 1291 | CG | PHE | 253 | -5.595 | -11.840 | -5.994 | 1.00 | 11.82 | A |
| ATOM | 1292 | CD1 | PHE | 253 | -4.385 | -11.175 | -6.231 | 1.00 | 13.69 | A |
| ATOM | 1293 | CD2 | PHE | 253 | -5.845 | -13.089 | -6.558 | 1.00 | 18.59 | A |
| ATOM | 1294 | CE1 | PHE | 253 | -3.364 | -11.771 | -6.993 | 1.00 | 14.39 | A |
| ATOM | 1295 | CE2 | PHE | 253 | -4.840 | -13.680 | -7.363 | 1.00 | 21.37 | A |
| ATOM | 1296 | CZ | PHE | 253 | -3.612 | -13.014 | -7.562 | 1.00 | 15.72 | A |
| ATOM | 1297 | C | PHE | 253 | -6.740 | -9.599 | -3.147 | 1.00 | 13.88 | A |
| ATOM | 1298 | O | PHE | 253 | -6.347 | -8.477 | -3.453 | 1.00 | 14.27 | A |
| ATOM | 1299 | N | THR | 254 | -7.865 | -9.837 | -2.502 | 1.00 | 14.00 | A |
| ATOM | 1300 | H | THR | 254 | -8.079 | -10.748 | -2.124 | 1.00 | 15.00 | A |
| ATOM | 1301 | CA | THR | 254 | -8.741 | -8.681 | -2.185 | 1.00 | 14.09 | A |
| ATOM | 1302 | CB | THR | 254 | -9.908 | -8.469 | -3.201 | 1.00 | 11.66 | A |
| ATOM | 1303 | OG1 | THR | 254 | -9.414 | -8.325 | -4.536 | 1.00 | 13.08 | A |
| ATOM | 1304 | HG1 | THR | 254 | -9.826 | -9.054 | -4.992 | 1.00 | 15.00 | A |
| ATOM | 1305 | CG2 | THR | 254 | -10.882 | -7.321 | -2.885 | 1.00 | 13.78 | A |
| ATOM | 1306 | C | THR | 254 | -9.270 | -8.779 | -0.738 | 1.00 | 12.36 | A |
| ATOM | 1307 | O | THR | 254 | -9.906 | -9.695 | -0.240 | 1.00 | 14.54 | A |
| ATOM | 1308 | N | SER | 255 | -9.007 | -7.683 | -0.027 | 1.00 | 13.42 | A |
| ATOM | 1309 | H | SER | 255 | -8.425 | -7.021 | -0.490 | 1.00 | 15.00 | A |
| ATOM | 1310 | CA | SER | 255 | -9.032 | -7.725 | 1.431 | 1.00 | 7.59 | A |
| ATOM | 1311 | CB | SER | 255 | -7.793 | -8.466 | 1.976 | 1.00 | 6.39 | A |
| ATOM | 1312 | OG | SER | 255 | -6.704 | -7.560 | 2.041 | 1.00 | 9.69 | A |
| ATOM | 1313 | HG | SER | 255 | -5.920 | -8.031 | 1.741 | 1.00 | 15.00 | A |
| ATOM | 1314 | C | SER | 255 | -9.248 | -6.341 | 2.085 | 1.00 | 10.05 | A |
| ATOM | 1315 | O | SER | 255 | -9.191 | -5.254 | 1.492 | 1.00 | 15.21 | A |
| ATOM | 1316 | N | PHE | 256 | -9.653 | -6.385 | 3.369 | 1.00 | 8.54 | A |
| ATOM | 1317 | H | PHE | 256 | -9.700 | -7.323 | 3.733 | 1.00 | 15.00 | A |
| ATOM | 1318 | CA | PHE | 256 | -10.114 | -5.168 | 4.035 | 1.00 | 7.94 | A |
| ATOM | 1319 | CB | PHE | 256 | -11.605 | -5.009 | 3.679 | 1.00 | 11.65 | A |

| ATOM | 1320 | CG | PHE | 256 | -12.376 | -3.824 | 4.235 | 1.00 | 8.72 | A |
|------|------|-----|-----|-----|---------|--------|--------|------|-------|---|
| ATOM | 1321 | CD1 | PHE | 256 | -11.766 | -2.570 | 4.533 | 1.00 | 11.20 | A |
| ATOM | 1322 | CD2 | PHE | 256 | -13.756 | -3.976 | 4.327 | 1.00 | 6.12 | A |
| ATOM | 1323 | CE1 | PHE | 256 | -12.503 | -1.490 | 5.034 | 1.00 | 11.49 | A |
| ATOM | 1324 | CE2 | PHE | 256 | -14.514 | -2.849 | 4.734 | 1.00 | 6.86 | A |
| ATOM | 1325 | CZ | PHE | 256 | -13.862 | -1.657 | 5.211 | 1.00 | 9.27 | A |
| ATOM | 1326 | C | PHE | 256 | -9.933 | -5.268 | 5.560 | 1.00 | 11.92 | A |
| ATOM | 1327 | O | PHE | 256 | -10.195 | -6.290 | 6.177 | 1.00 | 9.43 | A |
| ATOM | 1328 | N | GLY | 257 | -9.420 | -4.207 | 6.169 | 1.00 | 10.57 | A |
| ATOM | 1329 | H | GLY | 257 | -9.217 | -3.365 | 5.653 | 1.00 | 15.00 | A |
| ATOM | 1330 | CA | GLY | 257 | -9.368 | -4.406 | 7.612 | 1.00 | 11.26 | A |
| ATOM | 1331 | C | GLY | 257 | -8.965 | -3.122 | 8.287 | 1.00 | 11.14 | A |
| ATOM | 1332 | O | GLY | 257 | -8.916 | -2.068 | 7.679 | 1.00 | 10.81 | A |
| ATOM | 1333 | N | LEU | 258 | -8.688 | -3.277 | 9.565 | 1.00 | 12.61 | A |
| ATOM | 1334 | H | LEU | 258 | -8.776 | -4.204 | 9.943 | 1.00 | 15.00 | A |
| ATOM | 1335 | CA | LEU | 258 | -8.434 | -2.098 | 10.426 | 1.00 | 14.72 | A |
| ATOM | 1336 | CB | LEU | 258 | -9.751 | -1.212 | 10.704 | 1.00 | 14.67 | A |
| ATOM | 1337 | CG | LEU | 258 | -10.991 | -1.863 | 11.379 | 1.00 | 18.02 | A |
| ATOM | 1338 | CD1 | LEU | 258 | -12.317 | -1.125 | 11.094 | 1.00 | 15.05 | A |
| ATOM | 1339 | CD2 | LEU | 258 | -10.743 | -2.047 | 12.905 | 1.00 | 15.42 | A |
| ATOM | 1340 | C | LEU | 258 | -7.737 | -2.525 | 11.709 | 1.00 | 11.84 | A |
| ATOM | 1341 | O | LEU | 258 | -7.851 | -3.690 | 12.096 | 1.00 | 7.91 | A |
| ATOM | 1342 | N | LEU | 259 | -7.058 | -1.537 | 12.343 | 1.00 | 11.64 | A |
| ATOM | 1343 | H | LEU | 259 | -6.883 | -0.685 | 11.844 | 1.00 | 15.00 | A |
| ATOM | 1344 | CA | LEU | 259 | -6.581 | -1.780 | 13.714 | 1.00 | 9.53 | A |
| ATOM | 1345 | CB | LEU | 259 | -5.155 | -2.417 | 13.831 | 1.00 | 7.40 | A |
| ATOM | 1346 | CG | LEU | 259 | -4.194 | -1.621 | 12.931 | 1.00 | 11.40 | A |
| ATOM | 1347 | CD1 | LEU | 259 | -3.355 | -2.412 | 11.926 | 1.00 | 7.83 | A |
| ATOM | 1348 | CD2 | LEU | 259 | -3.379 | -0.670 | 13.808 | 1.00 | 13.30 | A |
| ATOM | 1349 | C | LEU | 259 | -6.652 | -0.497 | 14.531 | 1.00 | 10.40 | A |
| ATOM | 1350 | O | LEU | 259 | -6.202 | 0.556 | 14.082 | 1.00 | 9.73 | A |
| ATOM | 1351 | N | LYS | 260 | -7.193 | -0.629 | 15.762 | 1.00 | 12.00 | A |
| ATOM | 1352 | H | LYS | 260 | -7.395 | -1.553 | 16.115 | 1.00 | 15.00 | A |
| ATOM | 1353 | CA | LYS | 260 | -7.069 | 0.521 | 16.693 | 1.00 | 13.51 | A |
| ATOM | 1354 | CB | LYS | 260 | -8.014 | 0.312 | 17.885 | 1.00 | 13.49 | A |
| ATOM | 1355 | CG | LYS | 260 | -8.378 | 1.656 | 18.521 | 1.00 | 17.16 | A |
| ATOM | 1356 | CD | LYS | 260 | -9.435 | 1.456 | 19.596 | 1.00 | 12.01 | A |
| ATOM | 1357 | CE | LYS | 260 | -10.151 | 2.681 | 20.121 | 1.00 | 11.41 | A |
| ATOM | 1358 | NZ | LYS | 260 | -9.175 | 3.595 | 20.697 | 1.00 | 13.33 | A |
| ATOM | 1359 | HZ1 | LYS | 260 | -8.534 | 3.932 | 19.954 | 1.00 | 15.00 | A |
| ATOM | 1360 | HZ2 | LYS | 260 | -9.693 | 4.404 | 21.095 | 1.00 | 15.00 | A |
| ATOM | 1361 | HZ3 | LYS | 260 | -8.638 | 3.136 | 21.458 | 1.00 | 15.00 | A |
| ATOM | 1362 | C | LYS | 260 | -5.648 | 0.921 | 17.125 | 1.00 | 16.54 | A |
| ATOM | 1363 | O | LYS | 260 | -4.828 | 0.112 | 17.481 | 1.00 | 15.61 | A |
| ATOM | 1364 | N | LEU | 261 | -5.353 | 2.199 | 17.015 | 1.00 | 14.78 | A |
| ATOM | 1365 | H | LEU | 261 | -6.089 | 2.838 | 16.856 | 1.00 | 15.00 | A |
| ATOM | 1366 | CB | LEU | 261 | -3.705 | 4.005 | 17.185 | 1.00 | 19.53 | A |
| ATOM | 1367 | CG | LEU | 261 | -3.177 | 4.309 | 15.787 | 1.00 | 16.82 | A |
| ATOM | 1368 | CD1 | LEU | 261 | -3.010 | 5.779 | 15.767 | 1.00 | 12.45 | A |
| ATOM | 1369 | CD2 | LEU | 261 | -4.010 | 3.906 | 14.577 | 1.00 | 18.20 | A |
| ATOM | 1370 | C | LEU | 261 | -4.243 | 2.667 | 19.225 | 1.00 | 20.80 | A |
| ATOM | 1371 | OCT1 | LEU | 261 | -5.363 | 2.741 | 19.746 | 1.00 | 22.59 | A |
| ATOM | 1372 | OCT2 | LEU | 261 | -3.221 | 2.696 | 19.913 | 1.00 | 26.97 | A |
| ATOM | 1373 | CA | LEU | 261 | -4.122 | 2.604 | 17.684 | 1.00 | 18.13 | A |
| ATOM | 1374 | O | HOH | 501 | -20.040 | 9.837 | 7.596 | 1.00 | 16.33 | W |
| ATOM | 1375 | H1 | HOH | 501 | -19.411 | 10.547 | 7.803 | 1.00 | 10.00 | W |
| ATOM | 1376 | H2 | HOH | 501 | -19.615 | 9.317 | 6.900 | 1.00 | 10.00 | W |
| ATOM | 1377 | O | HOH | 502 | -9.727 | 11.545 | 10.743 | 1.00 | 10.94 | W |
| ATOM | 1378 | H1 | HOH | 502 | -10.039 | 11.934 | 9.919 | 1.00 | 15.00 | W |
| ATOM | 1379 | H2 | HOH | 502 | -10.233 | 12.125 | 11.315 | 1.00 | 15.00 | W |

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| ATOM | 1380 | O  | HOH | 503 | -8.158 | 13.188 | 13.681 | 1.00 | 30.64 | W |
|------|------|----|-----|-----|--------|--------|--------|------|-------|---|
| ATOM | 1381 | H1 | HOH | 503 | -8.715 | 12.529 | 13.277 | 1.00 | 15.00 | W |
| ATOM | 1382 | H2 | HOH | 503 | -8.700 | 13.944 | 13.574 | 1.00 | 15.00 | W |
| ATOM | 1383 | O  | HOH | 504 | -16.772 | 8.440 | 12.789 | 1.00 | 12.00 | W |
| ATOM | 1384 | H1 | HOH | 504 | -17.194 | 9.259 | 12.886 | 1.00 | 10.00 | W |
| ATOM | 1385 | H2 | HOH | 504 | -15.921 | 8.763 | 12.582 | 1.00 | 10.00 | W |
| ATOM | 1386 | O  | HOH | 505 | -25.173 | 7.297 | 7.925 | 1.00 | 47.03 | W |
| ATOM | 1387 | H1 | HOH | 505 | -24.690 | 8.064 | 8.239 | 1.00 | 10.00 | W |
| ATOM | 1388 | H2 | HOH | 505 | -25.990 | 7.684 | 7.583 | 1.00 | 10.00 | W |
| ATOM | 1389 | O  | HOH | 506 | -23.612 | 14.948 | 13.859 | 1.00 | 36.14 | W |
| ATOM | 1390 | H1 | HOH | 506 | -24.160 | 15.702 | 13.605 | 1.00 | 10.00 | W |
| ATOM | 1391 | H2 | HOH | 506 | -23.282 | 15.191 | 14.748 | 1.00 | 10.00 | W |
| ATOM | 1392 | O  | HOH | 507 | -17.329 | -8.460 | -7.186 | 1.00 | 34.02 | W |
| ATOM | 1393 | O  | HOH | 508 | -18.687 | -7.253 | -3.843 | 1.00 | 63.14 | W |
| ATOM | 1394 | O  | HOH | 509 | -7.157 | 11.327 | 3.239 | 1.00 | 22.26 | W |
| ATOM | 1395 | O  | HOH | 510 | -19.322 | 7.486 | -2.227 | 1.00 | 37.69 | W |
| ATOM | 1396 | O  | HOH | 511 | -14.645 | -7.711 | -1.931 | 1.00 | 26.48 | W |
| ATOM | 1397 | O  | HOH | 512 | -18.377 | -9.754 | 12.556 | 1.00 | 24.86 | W |
| ATOM | 1398 | O  | HOH | 513 | 0.030 | 0.048 | -13.455 | 1.00 | 26.05 | W |
| ATOM | 1399 | O  | HOH | 514 | -8.938 | 5.945 | 22.862 | 1.00 | 34.39 | W |
| ATOM | 1400 | O  | HOH | 515 | -29.446 | -4.922 | -7.247 | 1.00 | 41.61 | W |
| ATOM | 1401 | O  | HOH | 516 | -12.982 | 10.220 | 10.038 | 1.00 | 47.16 | W |
| ATOM | 1402 | O  | HOH | 517 | -21.797 | -9.377 | 7.242 | 1.00 | 60.65 | W |
| ATOM | 1403 | O  | HOH | 518 | -7.867 | 8.165 | 19.484 | 1.00 | 40.46 | W |
| ATOM | 1404 | O  | HOH | 520 | -15.588 | -14.701 | 14.628 | 1.00 | 63.80 | W |
| ATOM | 1405 | O  | HOH | 521 | -21.844 | 7.778 | 20.415 | 1.00 | 35.72 | W |
| ATOM | 1406 | O  | HOH | 522 | -6.555 | -3.308 | -15.790 | 1.00 | 33.63 | W |
| ATOM | 1407 | O  | HOH | 523 | -9.046 | -13.476 | -8.051 | 1.00 | 44.08 | W |
| ATOM | 1408 | O  | HOH | 524 | -17.413 | -9.311 | 17.071 | 1.00 | 34.06 | W |
| ATOM | 1409 | O  | HOH | 525 | -23.838 | 4.781 | 19.884 | 1.00 | 37.99 | W |
| ATOM | 1410 | O  | HOH | 526 | -26.323 | 15.525 | 10.379 | 1.00 | 72.49 | W |
| ATOM | 1411 | O  | HOH | 527 | -3.167 | -13.749 | -10.820 | 1.00 | 43.99 | W |
| ATOM | 1412 | O  | HOH | 528 | -0.470 | 2.513 | 17.943 | 1.00 | 63.68 | W |
| ATOM | 1413 | O  | HOH | 529 | -5.580 | -12.778 | -14.864 | 1.00 | 47.52 | W |
| ATOM | 1414 | O  | HOH | 530 | -2.641 | 7.004 | 2.495 | 1.00 | 18.07 | W |
| ATOM | 1415 | O  | HOH | 531 | -6.472 | 12.847 | 0.156 | 1.00 | 24.96 | W |
| ATOM | 1416 | O  | HOH | 532 | -10.363 | -16.426 | -0.360 | 1.00 | 63.56 | W |
| ATOM | 1417 | O  | HOH | 533 | -1.378 | -17.183 | -13.053 | 1.00 | 67.67 | W |
| ATOM | 1418 | O  | HOH | 534 | -4.774 | 9.073 | -0.651 | 1.00 | 23.36 | W |
| ATOM | 1419 | O  | HOH | 535 | -18.917 | -13.857 | 6.913 | 1.00 | 32.28 | W |
| ATOM | 1420 | O  | HOH | 536 | -23.062 | 3.270 | 0.454 | 1.00 | 52.03 | W |
| ATOM | 1421 | O  | HOH | 537 | -25.906 | 9.022 | 16.986 | 1.00 | 44.75 | W |
| ATOM | 1422 | O  | HOH | 538 | -21.729 | 16.972 | 17.027 | 1.00 | 53.12 | W |
| ATOM | 1423 | O  | HOH | 539 | -9.084 | 11.806 | 17.034 | 1.00 | 70.90 | W |
| ATOM | 1424 | O  | HOH | 540 | -10.938 | -13.296 | 15.207 | 1.00 | 35.65 | W |
| ATOM | 1425 | O  | HOH | 541 | -6.068 | 13.255 | 17.989 | 1.00 | 67.36 | W |
| ATOM | 1426 | O  | HOH | 542 | -20.593 | -11.039 | -9.003 | 1.00 | 96.30 | W |
| ATOM | 1427 | O  | HOH | 543 | -15.926 | 13.397 | 1.269 | 1.00 | 35.72 | W |
| ATOM | 1428 | O  | HOH | 544 | -24.591 | -7.285 | -2.353 | 1.00 | 43.42 | W |
| ATOM | 1429 | O  | HOH | 545 | -25.859 | -2.666 | -15.747 | 1.00 | 53.56 | W |
| ATOM | 1430 | O  | HOH | 546 | -23.074 | -1.533 | 11.026 | 1.00 | 56.44 | W |
| ATOM | 1431 | O  | HOH | 548 | -8.941 | -12.649 | -12.394 | 1.00 | 64.34 | W |
| ATOM | 1432 | O  | HOH | 549 | -14.150 | 6.038 | -12.250 | 1.00 | 41.38 | W |
| ATOM | 1433 | O  | HOH | 550 | -14.274 | -0.613 | 18.441 | 1.00 | 56.17 | W |
| ATOM | 1434 | O  | HOH | 551 | -12.241 | -19.609 | 8.637 | 1.00 | 80.90 | W |
| ATOM | 1435 | O  | HOH | 552 | -10.316 | 15.578 | 10.166 | 1.00 | 39.58 | W |
| ATOM | 1436 | O  | HOH | 553 | -15.367 | 10.941 | 14.659 | 1.00 | 40.40 | W |
| ATOM | 1437 | O  | HOH | 554 | -2.322 | 1.830 | -5.294 | 1.00 | 33.65 | W |
| ATOM | 1438 | O  | HOH | 555 | -22.393 | -14.875 | -4.217 | 1.00 | 52.40 | W |
| ATOM | 1439 | O  | HOH | 556 | -22.120 | 14.279 | 7.189 | 1.00 | 38.55 | W |

| ATOM | 1440 | O | HOH | 557 | -28.833 | 6.135 | 9.560 | 1.00 | 37.40 | W |
|------|------|---|-----|-----|---------|-------|-------|------|-------|---|
| ATOM | 1441 | O | HOH | 558 | -5.554 | -16.509 | 13.192 | 1.00 | 88.88 | W |
| ATOM | 1442 | O | HOH | 559 | -22.996 | 12.522 | 1.162 | 1.00 | 63.77 | W |
| ATOM | 1443 | O | HOH | 560 | -13.764 | 2.268 | -14.743 | 1.00 | 27.47 | W |
| ATOM | 1444 | O | HOH | 561 | -15.556 | 7.750 | -5.628 | 1.00 | 75.88 | W |
| ATOM | 1445 | O | HOH | 562 | -1.970 | -15.363 | -17.719 | 1.00 | 76.30 | W |
| ATOM | 1446 | O | HOH | 563 | -18.939 | -0.335 | -13.842 | 1.00 | 48.39 | W |
| ATOM | 1447 | O | HOH | 564 | -12.619 | 14.760 | -6.974 | 1.00 | 100.59 | W |
| ATOM | 1448 | O | HOH | 565 | -9.491 | 18.046 | 13.682 | 1.00 | 87.45 | W |
| ATOM | 1449 | O | HOH | 566 | -11.655 | -11.140 | 22.481 | 1.00 | 28.88 | W |
| ATOM | 1450 | O | HOH | 567 | -24.072 | -3.264 | -0.332 | 1.00 | 35.13 | W |
| ATOM | 1451 | O | HOH | 568 | -27.455 | 0.119 | -7.117 | 1.00 | 71.07 | W |
| ATOM | 1452 | O | HOH | 569 | -14.604 | 3.516 | -6.119 | 1.00 | 59.45 | W |
| ATOM | 1453 | O | HOH | 570 | -2.635 | -9.566 | -16.973 | 1.00 | 59.09 | W |
| ATOM | 1454 | O | HOH | 571 | -18.841 | 4.066 | -7.543 | 1.00 | 34.10 | W |
| ATOM | 1455 | O | HOH | 572 | -24.996 | 1.301 | 17.953 | 1.00 | 70.45 | W |
| ATOM | 1456 | O | HOH | 573 | -14.666 | 16.471 | 8.995 | 1.00 | 62.77 | W |
| ATOM | 1457 | O | HOH | 574 | -14.786 | 1.426 | 10.949 | 1.00 | 82.68 | W |
| ATOM | 1458 | O | HOH | 575 | -16.584 | -14.717 | -4.352 | 1.00 | 29.09 | W |
| ATOM | 1459 | O | HOH | 576 | -16.273 | -4.590 | 6.109 | 1.00 | 104.64 | W |
| ATOM | 1460 | O | HOH | 577 | -25.471 | -0.127 | -2.510 | 1.00 | 62.74 | W |
| ATOM | 1461 | O | HOH | 578 | -7.334 | -17.173 | 19.514 | 1.00 | 89.62 | W |
| ATOM | 1462 | O | HOH | 579 | -21.060 | 14.259 | 19.996 | 1.00 | 69.59 | W |
| ATOM | 1463 | O | HOH | 580 | -19.286 | 4.057 | -12.816 | 1.00 | 60.37 | W |
| ATOM | 1464 | O | HOH | 581 | -22.445 | -15.840 | 0.317 | 1.00 | 58.24 | W |
| ATOM | 1465 | O | HOH | 582 | -22.434 | -10.539 | 12.489 | 1.00 | 70.25 | W |
| ATOM | 1466 | O | HOH | 583 | -21.327 | 3.668 | -2.500 | 1.00 | 39.32 | W |
| ATOM | 1467 | O | HOH | 584 | -25.325 | 5.247 | 16.919 | 1.00 | 41.31 | ·W |
| ATOM | 1468 | O | HOH | 585 | -24.945 | -10.718 | -2.375 | 1.00 | 38.85 | W |
| ATOM | 1469 | O | HOH | 586 | -24.342 | -13.003 | 1.927 | 1.00 | 70.58 | W |
| ATOM | 1470 | O | HOH | 587 | -18.020 | 11.871 | 11.358 | 1.00 | 64.47 | W |
| ATOM | 1471 | O | HOH | 588 | -27.135 | 6.965 | 13.151 | 1.00 | 53.96 | W |
| ATOM | 1472 | O | HOH | 589 | -14.982 | -16.230 | -2.494 | 1.00 | 30.24 | W |
| ATOM | 1473 | O | HOH | 590 | -5.646 | 14.418 | -2.232 | 1.00 | 41.78 | W |
| ATOM | 1474 | O | HOH | 591 | -2.745 | -0.153 | -17.104 | 1.00 | 55.19 | W |
| ATOM | 1475 | O | HOH | 592 | -3.397 | -7.012 | 22.477 | 1.00 | 59.46 | W |
| ATOM | 1476 | O | HOH | 593 | -32.916 | -4.705 | -4.143 | 1.00 | 51.88 | W |
| ATOM | 1477 | O | HOH | 594 | -10.913 | -18.855 | -3.503 | 1.00 | 42.29 | W |
| ATOM | 1478 | O | HOH | 595 | -24.157 | 1.821 | -6.165 | 1.00 | 47.43 | W |

END

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WHAT IS CLAIMED IS:

1.    A method of preparing a crystal of CD40 ligand
      comprising the steps of:
      a)    providing an aqueous solution comprising a
            fragment of CD40 ligand;
      b)    providing a reservoir solution comprising a
            precipitating agent;
      c)    mixing a volume of said aqueous solution with a
            volume of said reservoir solution thereby forming
            a mixed volume; and
      d)    crystallizing at least a portion of said mixed
            volume.

2.    The method of claim 1 wherein the aqueous solution of
      CD40 ligand provided in step a) has a concentration of
      CD40 ligand of about 1 to about 50 mg per ml.

3.    The method of claim 2 wherein the aqueous solution has
      a concentration of CD40 ligand of about 5 mg per ml to
      about 15 mg per ml.

4.    The method of claim 3 wherein the aqueous solution has
      a concentration of CD40 ligand of about 10 mg per ml.

5.    The method of claim 1 wherein the precipitating agent
      is selected from the group consisting of sodium
      citrate, ammonium sulfate and polyethylene glycol.

6.    The  method of claim 1 wherein the concentration of the
      precipitating agent in the reservoir solution is about
      1.0 M to about 1.5 M.

7.    The method of claim 6 wherein the concentration of
      precipitating agent is about 1.2 M.

8.    The method of claim 1 wherein the pH of the reservoir

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solution is about 4 to about 10.

9.    The method of claim 8 wherein the pH is about 7.5.

10.   The method of claim 1 wherein step d) is by vapor
      diffusion crystallization, batch crystallization,
      liquid bridge crystallization or dialysis
      crystallization.

11.   A crystal formed by a functional fragment of the
      extracellular domain of CD40 ligand having
      approximately the following cell constants:
      a+b=77.17Å, c= 90.46Å, α = β =90°, γ = 120°, and a
      space group of R3.

12.   A crystal according to claim 11 described by the
      structural coordinates identified in Figure 10.

13.   A  machine readable data storage medium comprising a
      data storage material encoded with machine readable
      data which, when read by an appropriate machine, is
      capable of displaying a three dimensional
      representation of a crystal of a molecule or molecular
      complex comprising a fragment of CD40L having a binding
      site comprising amino acids Lys143, Arg203, Arg207 and
      Tyr145.

14.   A crystal of CD40 ligand (116-261) according to claim
      11, or a homolog thereof, wherein said crystal
      comprises a binding site, said binding site comprising
      amino acids Lys143, Arg203, Arg207 and Tyr145.

15.   A crystal according to claim 11 or a homolog thereof
      wherein said the crystal comprises Arg207 in close
      proximity to at least two hydrophobic residues.

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16. A crystal according to claim 14 wherein said crystal comprises at least 30 amino acids selected from the group consisting of: Ile127, Ser128, Glu129, Ala130, Ser131, Thr135, Ser136, Ala41, Lu142, Gly144, Tyr146, Cys178, Asn180, Ser185, Gln186, Ala187, Pro188, Ile190, Ala191, Ser192, Ser197, Pro198, Gly199, Arg200, Phe201, Glu202, Ile204, Ala209, Thr211, Pro217, Cys218, Gly219, Gln220, Glu230, Leu231, Gln232, Asn240, Val241, Thr242, Asp243, Ser245, Val247, Ser248, His249, Gly250, Thr251, Gly252 and Phe253.

17. A crystal according to claim 16, wherein said binding site comprises amino acids Ile127, Ser128, Glu129, Ala130, Ser131, Thr135, Ser136, Ala141, Glu142, Lys143, Gly144, Tyr145, Tyr146, Cys178, Asn180, Ser185, Gln186, Ala187, Pro188, Ile190, Ala191, Ser192, Ser197, Pro198, Gly199, Arg200, Phe201, Glu202, Arg203, Ile204, Arg207, Ala209, Thr211, Pro217, Cys218, Gly219, Gln220, Glu230, Leu231, Gln232, Asn240, Val241, Thr242, Asp243, Ser245, Val247, Ser248, His249, Gly250, Thr251, Gly252 and Phe253.

18. A method for determining at least a portion of a three dimensional structure of a molecular complex, said complex comprising at least a fragment of CD40 ligand, said method comprising the steps of:
   a.) determining the structural coordinates of a crystal of the fragment of CD40 ligand;
   b.) calculating phases from the structural coordinates;
   c) calculating an electron density map from the phases obtained in step b);
   d) determining the structure of at least a portion of the complex based upon said electron density map.

19. The method of claim 18 wherein the structural coordinates used in step a) are (1) substantially the same as those described in Table 1 or (2) describe substantially the same crystal as the coordinates in Table 1.

20. A method for evaluating the ability of a chemical entity to associate with CD40 ligand or CD40, a fragment of CD40 or CD40 ligand, or a complex comprising CD40 ligand, CD40, or homologs thereof, said method comprising the steps of:
a) employing computational or experimental means to perform a fitting operation between the chemical entity and said CD40 ligand or CD40, fragment or complex thereof, thereby obtaining data related to said association; and
b) analyzing the data obtained in step a) to determine the characteristics of the association between the chemical entity and said CD40 ligand or CD40, fragment or complex.

21. A chemical entity identified by the method of claim 20, wherein said chemical entity is capable of interfering with the in vivo or in vitro association between CD40 and CD40L.

22. A chemical entity identified by the method of claim 20, wherein said chemical entity is capable of associating with a binding site on CD40L, said binding site comprising amino acids Lys143, Arg203, Arg207 and Tyr145.

23. A chemical entity identified by the method of claim 20 wherein said chemical entity is capable of associating with CD40, and comprises a binding site comprising

amino acids Lys143, Arg203, Arg207 and Tyr145.

24. The chemical entity identified by the method of claim
    22 or 23 wherein said CD40L binding site comprises at
    least 30 amino acids selected from the group consisting
    of: Ile127, Ser128, Glu129, Ala130, Ser131, Thr135,
    Ser136, Ala141, Glu142, Gly144, Tyr146, Cys178, Asn180,
    Ser185, Gln186, Ala187, Pro188, Ile190, Ala191, Ser192,
    Ser197, Pro198, Gly199, Arg200, Phe201, Glu202, Ile204,
    Ala209, Thr211, Pro217, Cys218, Gly219, Gln220, Glu230,
    Leu231, Gln232, Asn240, Val241, Thr242, Asp243, Ser245,
    Val247, Ser248, His249, Gly250, Thr251, Gly252 and
    Phe253.

25. The chemical entity of claim 23, wherein said entity is
    capable of associating with a binding site on CD40L,
    wherein said binding site comprises amino acids Ile127,
    Ser128, Glu129, Ala130, Ser131, Thr135, Ser136, Ala141,
    Glu142, Lys143, Gly144, Tyr145, Tyr146, Cys178, Asn180,
    Ser185, Gln186, Ala187, Pro188, Ile190, Ala191, Ser192,
    Ser197, Pro198, Gly199, Arg200, Phe201, Glu202, Arg203,
    Ile204, Arg207, Ala209, Thr211, Pro217, Cys218, Gly219,
    Gln220, Glu230, Leu231, Gln232, Asn240, Val241, Thr242,
    Asp243, Ser245, Val247, Ser248, His249, Gly250, Thr251,
    Gly252 and Phe253.

26. A heavy atom derivative of a crystallized form of CD40
    ligand.

27. A heavy atom derivative of  the crystal of claim 11.

28. The use of the structural coordinates of CD40 ligand,
    or portions thereof, to solve a    crystal form of a
    mutant, homologue or co-complex of CD40 ligand or a
    fragment thereof by molecular replacement.

29. A method of computationally or experimentally evaluating a chemical entity to obtain information about its association with the binding site of CD40 ligand using a crystal of CD40 ligand or the structural coordinates thereof.

30. The method of claim 29 wherein the crystal has the structural coordinates described in Table 1.

31. The use of the structural coordinates of a crystal, wherein said crystal is substantially the same as the crystal of CD40 ligand described by the coordinates in Table 1.

32. The method of claim 29 wherein said crystal is a crystal according to claim 11.

33. The use of the structural coordinates of a crystal according to claim 31, to identify, characterize or design chemical entities having a desired association with a CD40 ligand, or fragment thereof.

34. The method of claim 33 further comprising the step of optimizing the binding characteristics of the chemical entity identified, characterized, or designed.

35. The method of claim 34 further comprising the step of determining the orientation of ligands in a binding site of CD40 ligand.

36. A chemical entity identified or designed according to claim 33.

37. The use of a CD40 ligand crystal to determine binding interactions between a chemical entity and CD40 ligand.

38.   The use according to claim 37 wherein said CD40 ligand
      crystal is the crystal of claim 11.
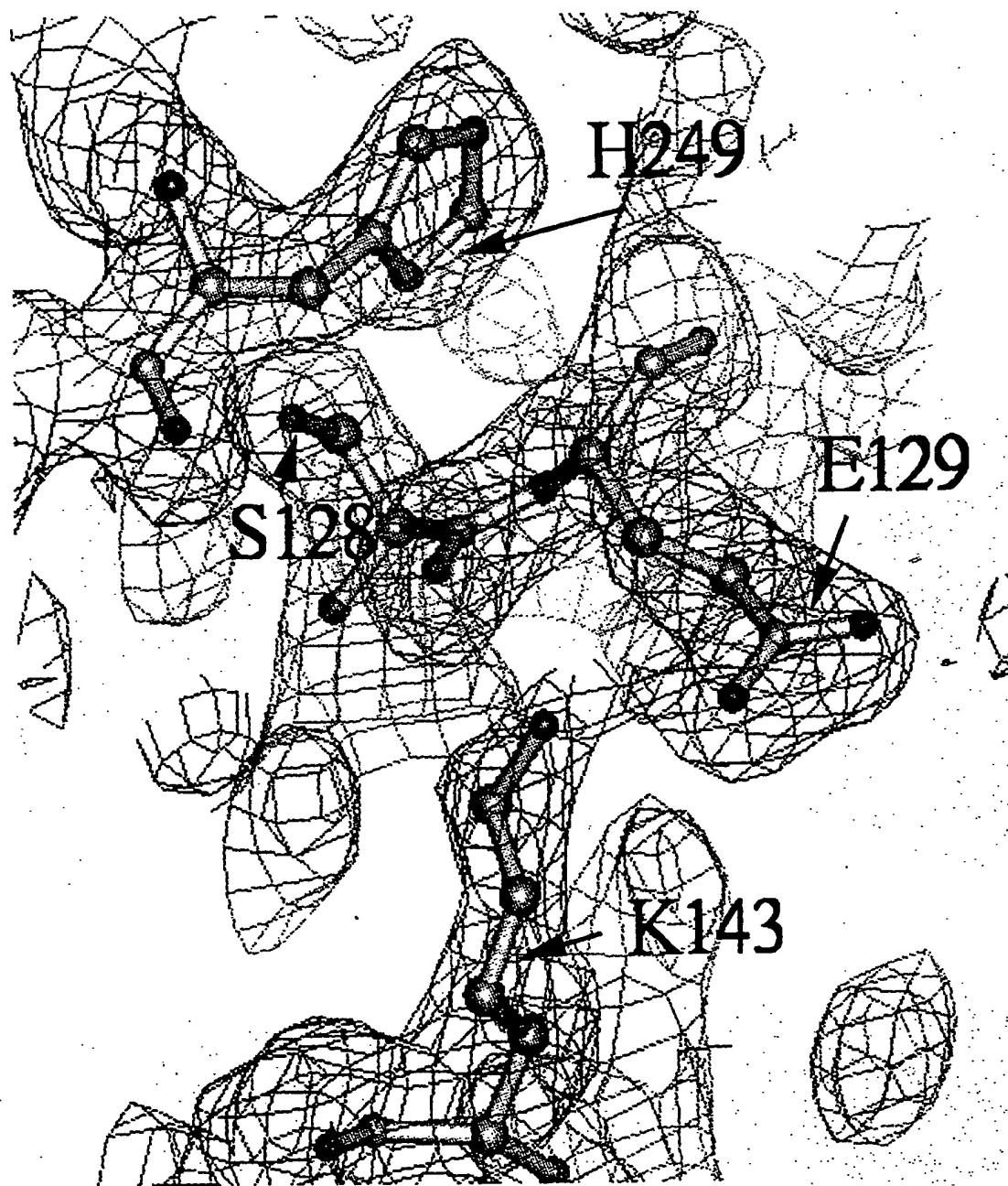
FIG. 1
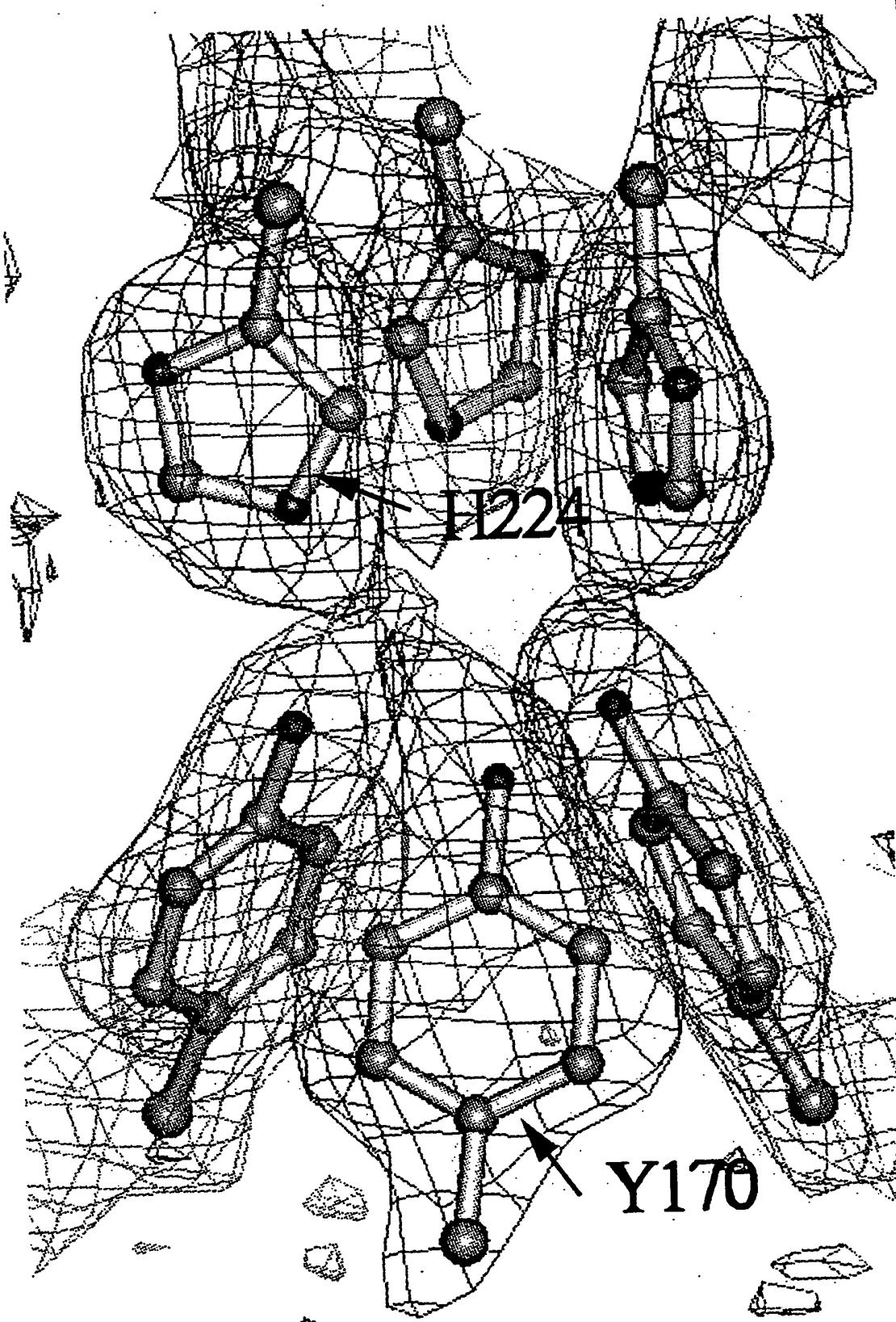
FIG. 2
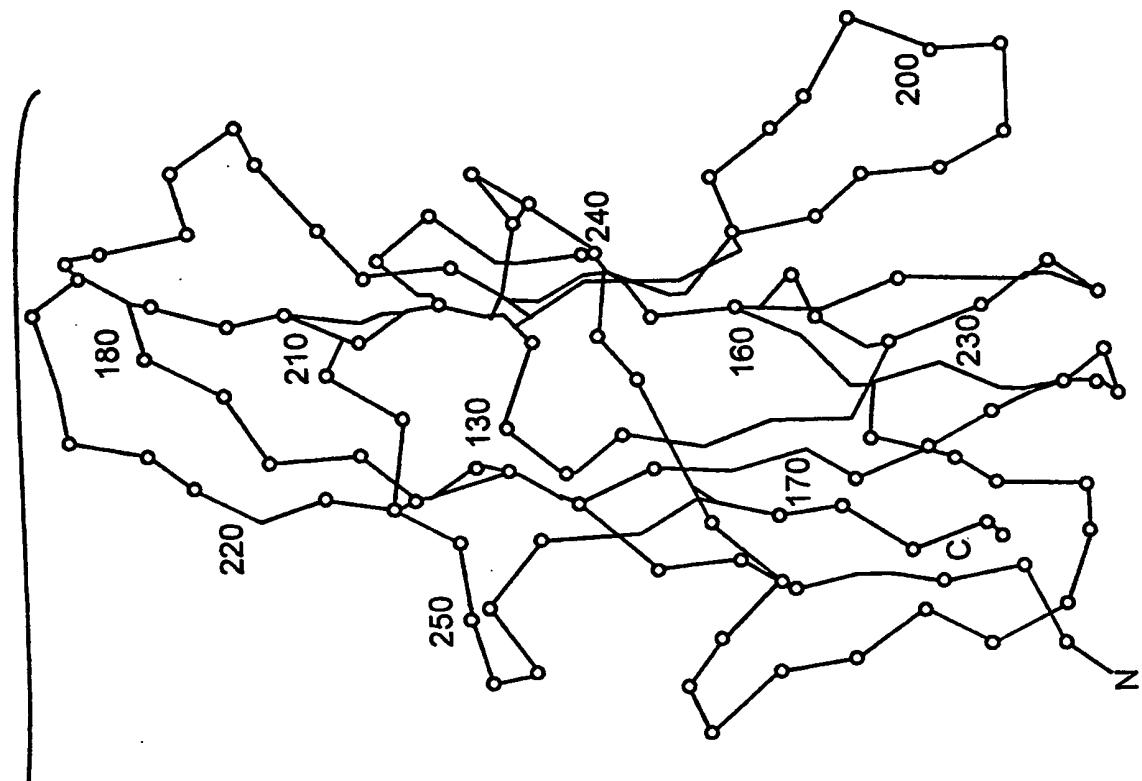
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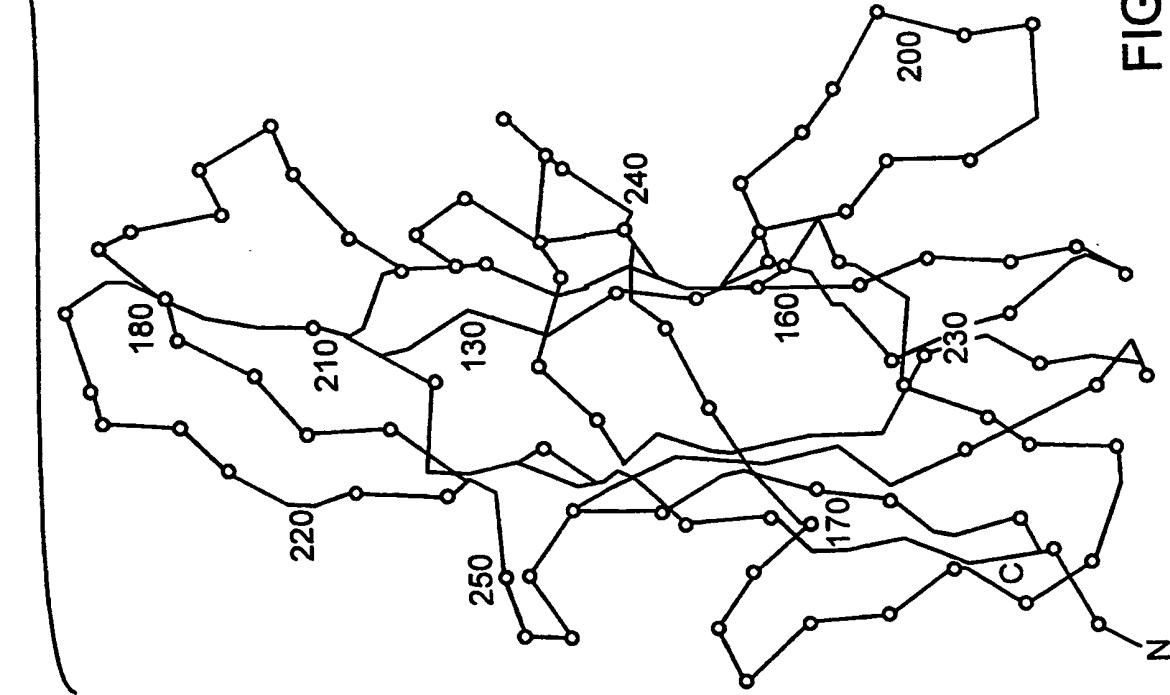
FIG. 4

```
            ---A--          --A"--      ----B'----   --B-
        115      125     135      145        155
TNFa:RTPSDKP  VAHVVANPQAEGQ  LQWLNRRANALLANGV  ELRD NQLVVP
LTa:    TLKP  AAHLIGDPSKQNS  LLWRANTDRAFLQDGF  SLSN NSLLVP
CD40L: GDQNPQIAAHVISEASSKTTSVLQW  AEKGYYTMSNNLVTLENGKQLTVK
(1)              *   ** *       *******
(2)      .........-..-.--.+...+....-...---......-..........


        -----C-----------    ----D----    -----E----
    165       175        185      195        205
 SEGLYLIYSQVLFKGQGCP  STHV LLTHTISRIAVSYQTKVNLLSAIKSPCQR
 TSGIYFVYSQVVFSGKAYSPKATSSPL YLAHEVQLFSSQYPFHVPLLSSQKMVY
 RQGLYYIYAQVTF   CSNREASSQAPFIASLCLKSPGRFE RI LLRAANTHS S
             ***       **  *     ***** *     * *
 ....................+..................++...........-....


        -----F-----------   --G---         ---H---
   215         225       235      245        255
 ETPEGAEAKPWYEPIYLGGVFQLEKGDRLSAEINRPDYLLFAESGQVY  FGIIAL
    PGLQE  PWLHSMYHGAAFQLTQGDQLSTHTDGIPHLVLSPST VF  FGAFAL
 AKPCGQ        QSIHLGGVFELQPGASVFVNVTDPSQV  SHGT GFTSFGLLKL
       *     *  *              * *  ***** *
 ................-.......-....+..+...............-...
```

# FIG. 5
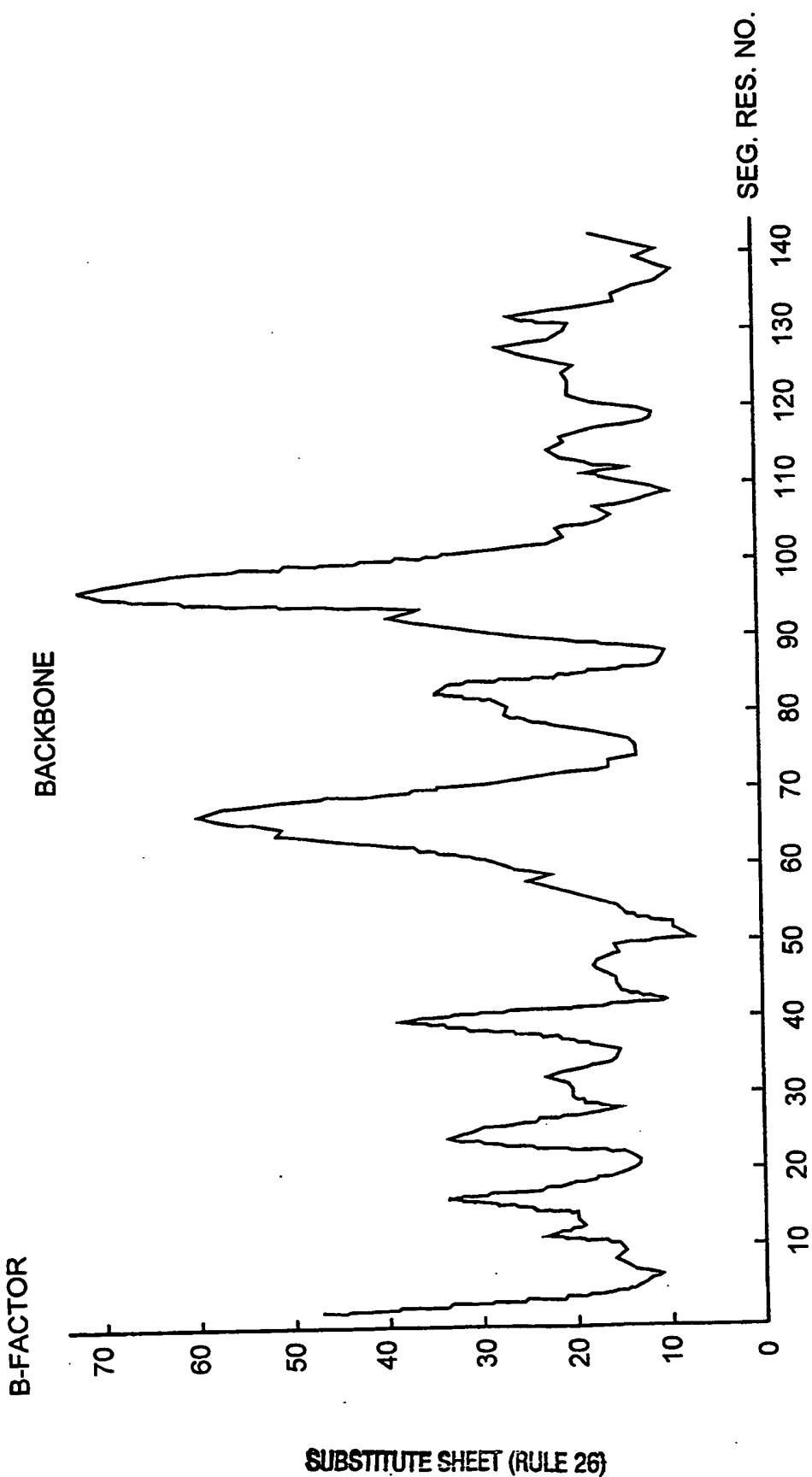
FIG. 6

FIG. 7

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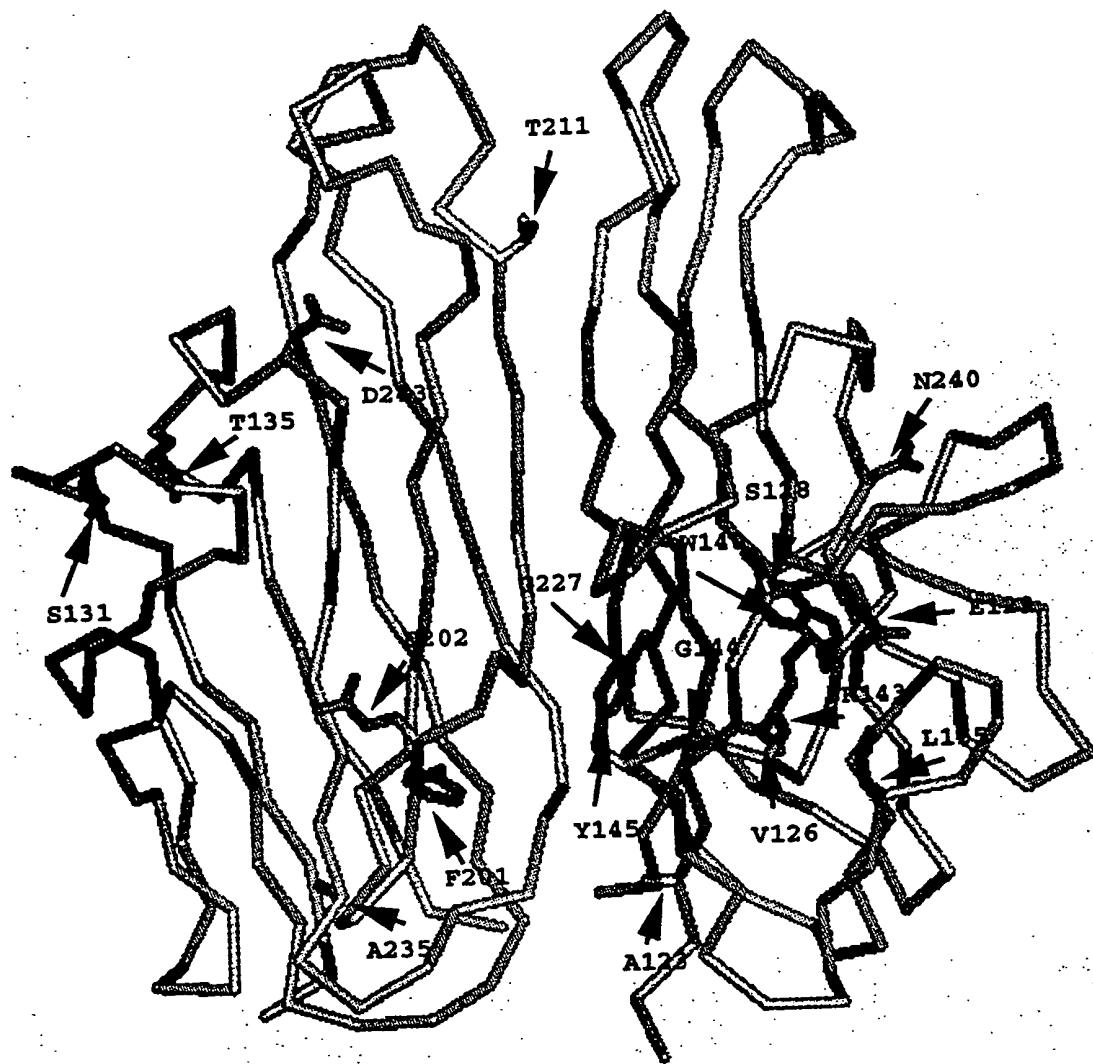
CRYSTALLOGRAPHIC AND REFINEMENT DATA:

SYMMETRY:           R3

UNIT CELL:          $a = b = 77.17$ Å, $c = 90.46$ Å, $\alpha = \beta = 90°$, $\gamma = 120°$

NO. OF CRYSTALS:    1

RESOLUTION:         1.75 Å

REFLECTIONS         42,587
(MEASURED):

REFLECTIONS         15,693
(UNIQUE):

$R_{MERGE}$a:       6.7%

COMPLETENESS        77.1%
(OVERALL):

COMPLETENESS        89.9%
(TO 2.1Å):

$R_{WORK}$b:        21.8%  FOR 7.5-2 Å DATA

$R_{FREE}$b:        29.1%

R.M.S DEVIATIONS
    BONDS:          0.021 Å
    ANGLES:         3.9°

-----------------------------------------------------------------------------

a) $R_{sym} = \Sigma |I_{obs} - <I>| / \Sigma <I>$

b) $R_{free} = R_{work} = \Sigma |F_{obs} - F_{calc}| / \Sigma F_{obs}$

"FREE" AND "WORK" REFER TO THE FREE AND WORKING DATA SETS, RESPECTIVELY.

# FIG. 8

Intern ⸱⸱nal Application No

PCT/US 96/10664

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6    C07K14/725    C07K14/525    C07K1/00    G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6    C07K    G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP,A,0 585 943 (BRISTOL-MYERS SQUIBB COMPANY) 9 March 1994 see the whole document --- | 21-26,36 |
| X | EP,A,0 555 880 (BRISTOL-MYERS SQUIBB COMAPNY) 18 August 1993 see the whole document --- | 21-26,36 |
| X | WO,A,94 17196 (IMMUNEX COPRPORATION) 4 August 1994 see the whole document --- | 21-26,36 |
| X | WO,A,93 08207 (IMMUNEX CORPORATION) 29 April 1993 see the whole document --- | 21-26,36 |
|  | -/-- |  |

☒ Further documents are listed in the continuation of box C.    ☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 29 October 1996 | 1 5. 11. 96 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016 | Masturzo, P |

page 1 of 2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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| P,X | BIOCHEMISTRY, vol. 34, no. 31, 8 August 1995, EASTON, PA US, pages 9884-9892, XP002017168 J BAJORATH ET AL.: "Analysis of gp39/CD40 interactions using molecular models and site-directed mutagenesis" see the whole document --- | 13, 21-26, 28-38 |
| P,X | CHEMICAL ABSTRACTS, vol. 123, no. 23, 4 December 1995 Columbus, Ohio, US; abstract no. 311922s, M KARPUSAS ET AL.: "2A crystal structure of an extracellular fragment of human CD40 ligand" page 700; XP002017170 see abstract & STRUCTURE, vol. 3, no. 10, 1995, LONDON, pages 1031-1039, ----- | 1-38 |

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